Journal of Saudi Chemical Society (2016) **xxx**, xxx–xxx

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles

Adnan Çetin [a], **İshak Bildirici** [b,*]

[a] *Muş Alparslan University, Faculty of Education, Department of Sciences, Muş, Turkey*
[b] *Yüzüncü Yıl University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Van, Turkey*

Received 21 April 2016; revised 23 May 2016; accepted 31 May 2016

KEYWORDS

Pyrazole;
Pyrazolo-pyridazine;
Furandione;
Oxazine;
Pyrrole;
Chromone;
Antibacterial activity

Abstract 4-Acyl-pyrazole-3-carboxylic acids (**1**) were synthesized via the reaction of 4-acyl-2,3-furandiones (**F**) with hydrazone (1-benzylidene-2-(2,5-dimethyl-phenyl)-hydrazine) by heating under solid phase and their acid chlorides (**2**) were obtained. Then these derivatives were easily converted into the corresponding derivatives such as ester, amide, ureide, pyrazolo-pyridazine, etc. Totally 62 new compounds were synthesized. The structures of these new synthesized compounds were determined by spectroscopic methods and the *in vitro* antibacterial activity of newly synthesized compounds were carried out against some gram-positive and gram-negative bacteria by well diffusion method (zone inhibition). Our results have showed that these new synthesized compounds have much potent of antibacterial activity owing to containing of pyrazole and/or pyridazine, chromone, oxazine, furane, and pyrrole rings. Some of the new pyrazole derivatives exhibited higher activities than reference drugs against the representative bacteria.

1. Introduction

Natural antibiotic compounds used in the treatment and prevention of bacterial infection have become necessary for the current health care system, assisting and complementing the natural immune system against microbial pathogens. However, because conventional antibiotics are often abused/over-used to treat microbial infections, some microorganisms have developed resistance to some of these antibiotics [1]. So the medical communities are faced in a serious problem with antimicrobial and antibiotic resistance, so much as to prompt the World Health Organization (WHO) to classify antimicrobial resistance as a "serious threat that is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country" ("WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health" The World Health Organization, April 30, 2014. Retrieved December 21, 2014.). These bacterial strains that are resistant to conventional antibacterial therapies have prompted the development of novel efficient antibiotic agents that are alternatives to conventional antibacterial therapies [2,3].

* Corresponding author.
E-mail addresses: ishak@yyu.edu.tr, ishakbildirici@gmail.com (İ. Bildirici).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.05.008

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008

On the other hand, the pyrazole ring that contains a five-membered heterocyclic organic compound with two adjacent nitrogen atoms is a prominent heterocyclic scaffold in lots of bioactive molecules. They are important substances and have gained widespread attention in agrochemical, pharmaceutical and chemical industries [4]. They possess a wide range of biological activities [5–8], including antimicrobial [9–16], antiviral [17–20], anticancer [21,22], antiinflammatory [23–26], antihistaminic [27], pesticidal [28], antifungal [29–31], against rheumatoid arthritis [32], anticonvulsant [33], antidepressant [34], antipyretic [35,36], antibacterial [37,38] agents, etc. and these bio-activities have inspired chemists to synthesize substituted pyrazole systems to explore the usefulness of this heterocyclic template. In recent years, a number of pyrazole-containing compounds have been successfully commercialized such as the blockbuster drugs Viagra (Sildenafil inhibits phosphodiesterase) [39], Celebrex [40] (Celecoxib demonstrates antiinflammation effect and inhibits COX-2), Rimonabant (trade name Acomplia) functions as cannabinoid receptor and is utilized in obesity treatment, Fomepizole (It is on the World Health Organization's List of Essential Medicines) inhibits alcohol dehydrogenase, Ceftolozane (Zerbaxa) is a 5th generation cephalosporin antibiotic (Food and Drug Administration approved on 2014), Pyrazomycin (Pyrazofurin) antiviral agents, hormone oxytocin agonists (WAY-VNA-932). Moreover, some pyrazole-containing compounds are used as α-Helix mimetic [41] and applied as ligands for the transition-metal-catalyzed cross-coupling reactions [42,43] (Fig. 1).

As a matter of fact, pyrazole derivatives have been studied for a long time as an important class of heterocyclic compounds and still continue to attract considerable attention according to all this information. Hence, these ones are popular targets for synthetic chemists. Classic methods for the synthesis of pyrazoles involve the approaches based either on the condensation of hydrazines with 1,3-dicarbonyl compounds [44,45] and their 1,3-dielectrophilic equivalents including α,β-unsaturated aldehydes and ketones [46] or on the intermolecular 1,3-dipolar cycloaddition of diazoalkanes and nitrilimines with alkenes and alkynes [47,48]. A simple and effective procedure in the preparation of pyrazole derivatives is the nucleophilic addition of hydrazines to 4-acyl-5-phenyl-2,3-furandiones **F** [49] in various solvent or solventless [50–53].

In addition, heterocyclic scaffolds such as pyridazine, chromone, oxazine, furane and pyrrole derivatives have various and valuable biological activities such as antimicrobial, anticancer, anti-HIV and antimalarial properties [54–58].

Within the present study, we prepared a series of 4-acyl-pyrazole containing aforementioned active pharmacophores in order to incorporate them in a novel single molecule. Besides, we aimed to report (1) synthesis, (2) characterization of unknown analogs of 4-acyl-pyrazole derivatives and (3) antibacterial activities of newly synthesized 4-acyl-pyrazoles against representative gram-negative and gram-positive bacteria. Hence, this work might be a precious *original mini review* for pyrazole chemistry particularly for 4-acyl-pyrazole derivatives and their bioactivities.

2. Experimental

2.1. Materials and methods

All reagents and solvents were of reagent grade quality and were obtained from commercial suppliers. All solvents were dried by refluxing with appropriate drying agents and distilled before use. Follow up of the reactions and checking the purity of the compounds was made and tested in each step by TLC (SiO_2) using a DC Alufolien Kieselgel 60 F 254 Merck. Compounds were visualized by Camag TLC devices UV (254/366 nm). Melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on Thermo Scientific Flash 2000. The FT-IR spectra were obtained as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Instrument Avance Series-Spectrospin DPX-400 Ultra Shield, using TMS as an internal standard. Chemical shifts are given in δ, ppm. Splitting patterns were designated as follows: s: singlet; *d*: doublet; *t*: triplet; *q*: quartet; *m*: multiplet; and br: broad. The mass spectrum was measured on Agilent LC/MSD spectrometers.

2.2. Synthesis of compounds

2.2.1. 4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (*1a*)

An equimolar mixture of furandione **F** (0.278 g, 1 mmole) and 1-benzylidine-2-(2,5-dimethylphenyl)hydrazine (0.224 g, 1 mmole) were reacted in solid phase for approximately 40 min. The oily residue obtained was treated with dry ether. The crude product formed was crystallized from an ethyl alcohol to give 0.38 g (75%) of **1a**, mp 202 °C; IR (ν, cm^{-1}): 3271 (O—H, COOH), 3040 (aromatic C—H), 2921 (aliph. C—H),

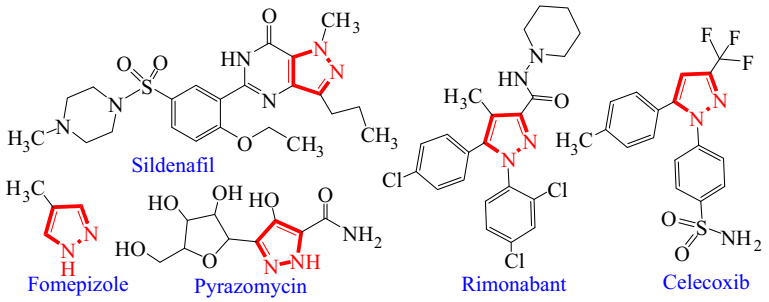


Figure 1 Some commercialized pyrazole-containing compounds.

1720 (C═O, COOH), 1659 (C═O, benzoyl), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.10 (br, 1H, —OH), 7.77–6.96 (m, 13H, Ar—H), 2.23 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 191.42 (C═O, benzoyl), 162.75 (C═O, COOH), 144.48 (C_3), 143.67 (C_5), 142.33, 141.31, 138.91, 138.32, 138.04, 133.14, 130.73, 130.57, 129.70, 129.46, 129.30, 129.06, 128.78, 127.68, 127.89, 109.21 (C_4), 18.85, 14.19 (—CH_3). Anal. Cal. for $C_{26}H_{20}N_2O_3$ (396,44 g/mol): C, 75.74; H, 5.08; N, 7.07. Found: C, 75.67; H, 5.11; N, 7.15.

2.2.2. 1-(2,5-Dimethylphenyl)-4-(ethoxycarbonyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (*1b*)

An equimolar mixture of furandione **F** (0.246 g, 1 mmole) and 1-benzylidine-2-(2,5-dimethylphenyl)hydrazine (0.224 g, 1 mmole) were reacted solid phase for approximately 40 min. The oily residue obtained was treated with dry ether. The crude product formed was crystallized from a toluene to give 0.31 g (65%) of **1b**, mp 202 °C, IR (ν, cm^{-1}): 3246 (O—H, COOH), 3066 (aromatic C—H), 2918 (aliph. C—H), 1732 (C═O, ester), 1710 (C═O, COOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.88 (br, 1H, —OH), 7.97–6.81 (m, 8H, Ar—H), 4.18 (q, 2H, —CH_2), 2.19, 1.85 (s, 3H, Ar—CH_3), 1.31 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.16 (C═O, ester), 166.09 (C═O, COOH), 145.59 (C_3), 144.37 (C_5), 143.60, 136.39, 135.49, 133.32, 132.10, 130.85, 129.73, 129.62, 129.30, 128.92, 128.45, 127.24, 114.19 (C_4), 60.73 (O—CH_2), 21.50, 17.50 (Ar—CH_3), 14.30 (-CH_3). Anal. Cal. for $C_{21}H_{20}N_2O_4$ (364,39 g/mol): C, 69.22; H, 5.53; N, 7.69. Found: C, 69.15; H, 5.50; N, 7.74.

2.2.3. 4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl chloride (*2a*)

Compound **1a** (0.397 g, 1 mmole) was refluxed with excessive $SOCl_2$ at 80 °C for about 7 h. Excessive $SOCl_2$ was evaporated. Remaining oily product was purified in dry ether/cyclohexane mixture, which was crystallized from n-hexane/cyclohexane, to yield 0.31 g (60%); mp 145 °C; IR (ν, cm^{-1}): 3045 (aromatic C—H), 2920 (aliph. C—H), 1720 (C═O, acyl), 1664 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08–6.42 (m, 13H, Ar—H), 2.09, 1.75 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 193.12 (Ph—C═O), 167.77 (—COCl), 143.46 (C_3), 137.33 (C_5), 135.96, 135.33, 133.33, 132.47, 132.24, 131.70, 130.41, 129.99, 129.74, 129.38, 128.81, 128.70, 128.25, 127.43, 126.88, 121.50 (C_4), 22.99, 14.05 (Ar—CH_3). Anal. Cal. for $C_{25}H_{19}ClN_2O_2$ (414,88 g/mol): C, 72.37; H, 4.62; N, 6.75. Found: C, 72.29; H, 4.61; N, 6.83.

2.2.4. Ethyl 3-(cholorocarbonyl)-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate (*2b*)

Compound **1b** (0.397 g, 1 mmole) was refluxed with excessive $SOCl_2$ at 80 °C for about 7 h. Excessive $SOCl_2$ was evaporated. Remaining oily product was purified in dry ether which was crystallized from toluene, to yield 0.31 g (65%), mp 118 °C; IR (ν, cm^{-1}): 3090 (aromatic C—H), 2924 (aliph. C—H), 1723 (C═O, acyl), 1659 (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64–6.54 (m, 8H, Ar—H), 4.22 (q, 2H, —CH_2), 2.28, 1.73 (s, 3H, Ar—CH_3), 1.42 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.34 (C═O, acyl), 164.50 (C═O, ester), 145.16 (C_3), 144.32 (C_5), 143.56, 136.79, 135.92, 134.14, 132.35, 131.44, 130.36, 129.70, 129.31, 128.38, 127.41, 126.16, 113.48 (C_4), 61.28 (O—CH_2), 24.20, 19.15 (Ar—CH_3), 15.70 (—CH_3). Anal. Cal. for $C_{21}H_{19}ClN_2O_3$ (382,84 g/mol): C, 65.88; H, 5.00; N, 7.32. Found: C, 65.78; H, 5.02; N, 7.41.

2.2.5. General procedure for synthesis of ester

Compound **3a–b** can be synthesized in two different methods.

Method A: To the cold solution of the pyrazole acid **1a** (0.397 g, 1 mmole) in sulfuric acid was added a large excess of methanol with stirring. Then the reaction mixture was refluxed on a steam bath for 4 h with stirring. After cooling the precipitate formed was filtered off and crystallized from the same alcohol to give **3a–b.**

Method B: The acid chloride **2a** (0.414 g, 1 mmole) and a moderate excess of the methyl alcohol were refluxed together with a catalytic amount of pyridine for 3 h. After cooling, the solution was acidified by adding diluted hydrochloric acid (12%) to give a crude solid that was crystallized from methyl alcohol.

*2.2.5.1. Methyl 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**3a**).* The yield was 0.35 g (85%), mp 180 °C; IR (ν, cm^{-1}): 3100 (aromatic C—H), 2951 (aliph. C—H), 1723 (C═O, ester), 1663 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87–6.46 (m, 13H, Ar—H), 3.75 (s, 3H, —OCH_3), 2.11, 1.75 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.39 (C═O, benzoyl), 161.77 (C═O, ester), 144.81 (C_3), 143.29 (C_5), 142.06, 138.11, 136.29, 135.31, 133.30, 132.34, 129.96, 129.31, 128.57, 128.50, 128.25, 127.55, 126.82, 122.01, 107.15 (C_4), 52.18 (—CH_3), 18.91, 17.33 (Ar—CH_3). Anal. Cal. for $C_{26}H_{22}N_2O_3$ (410,46 g/mol): C, 76.08; H, 5.40; N, 6.82. Found: C, 75.97; H, 5.37; N, 6.91.

*2.2.5.2. Ethyl 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carboxylate (**3b**).* Compound **3b** was obtained in 70% yield (0.31 g) by method A and B. IR (ν, cm^{-1}): 3100 (aromatic C—H), 2924 (aliph. C—H), 1718 (C═O, ester), 1666 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89–6.93 (m, 13H, Ar—H), 4.19 (q, 2H, -OCH_2), 2.2, 1.7 (s, 3H, Ar—CH_3), 1.07 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.44 (C═O, benzoyl), 161.29 (C═O, ester), 144.81 (C_3), 143.29 (C_5), 142.35, 140.51, 139.42, 138.51, 135.61, 133.29, 132.34, 131.35, 130.04, 129.37, 128.56, 128.51, 128.24, 127.63, 126.81, 121.71 (C_4), 61.35 (O—CH_2), 18.93, 17.37 (Ar—CH_3), 13.80 (—CH_3). Anal. Cal. for $C_{27}H_{24}N_2O_3$ (424,49 g/mol): C, 76.39; H, 5.70; N, 6.60. Found: C, 76.32; H, 5.73; N, 6.65.

2.2.6. 4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carboxamide (*3c*)

A moderate stream of gaseous ammonia was allowed to bubble through a solution of pyrazole-3-carboxylic acid chloride **2a** (0.414 g, 1 mmole) in 20 mL hexane during 30 min with ice-cooling. Then the crude precipitate was isolated by filtration and crystallized from methanol to give 0.29 g (70%) of **3c**, mp 293 °C; IR (ν, cm^{-1}): 3434 (—NH_2), 3080 (aromatic C—H), 2910 (aliph. C—H), 1693 (C═O, benzoyl), 1664 (C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89–6.93 (m, 8H, Ar—H), 5.46 (b, 2H, —NH_2), 2.14, 1.82 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 192.90

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008

(C═O, benzoyl), 163.29 (C═O, amide), 146.69 (C_3), 142.51 (C_5), 137.91, 137.46, 136.24, 133.33, 131.76, 130.78, 129.60, 129.54, 129.41, 129.25, 129.10, 128.32, 128.13, 127.70, 120.95 (C_4), 20.74, 17.12 (Ar—CH_3). Anal. Cal. for $C_{25}H_{21}N_3O_2$ (395,45 g/mol): C, 75.93; H, 5.35; N, 10.63. Found: C, 75.84; H, 5.37; N, 10.69.

*2.2.7. 4-Benzoyl-1-(2,5-dimethylphenyl)-N,5-diphenyl-1H-pyrazole-3-carboxamide (**3d**)*

An equimolar mixture of the acid chloride **2a** (0.414 g, 1 mmole) and *n*-phenyl amine (1 mmole) was refluxed in xylene for 4 h. After evaporation, the oily residue was treated with dry ether and the formed crude product was crystallized from ether/chloroform. The yield 0.3 g (60%), mp 205 °C; IR (ν, cm^{-1}): 3224 (-NH), 3040 (aroma. C—H), 2910 (aliph. C—H), 1693 (C═O, benzoyl), 1664 (C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.02 (b, 1H, NH), 7.88–6.73 (m, 13H, Ar—H), 2.18, 1.75 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.56 (C═O, benzoyl), 163.61 (C═O, amide), 145.60 (C_3), 142.18 (C_5), 137.63, 136.66, 133.70, 133.64, 132.36, 131.93, 131.39, 129.60, 129.56, 129.40, 129.38, 129.25, 129.29, 128.56, 128.20, 127.60, 126.12, 122.21 (C_4), 21.70, 17.37 (Ar—CH_3). Anal. Cal. for $C_{31}H_{25}N_3O_2$ (471,55 g/mol): C, 78.96; H, 5.34; N, 8.91. Found: C, 78.85; H, 5.32; N, 8.91.

*2.2.8. 4-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carboxamido)- benzene-sulfonic acid (**3e**)*

A miliequimolar mixture of compound **2a** and 4-aminobenzenesulfonic acid were refluxed in toluene for 6 h. After the solvent was removed by evaporation, the oily residue was treated with ether and the crude product formed was crystallized from methanol. The yield was 0.23 g (40%), mp 222 °C; IR (ν, cm^{-1}): 3100 (aromatic C—H), 2922 (aliph. C—H), 1669 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.02 (s, 1H, —NH), 8.82–6.88 (m, 17H, Ar—H), 2.36 (b, 1H, —OH), 2.2, 1.85 (s, 3H, Ar—CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.76 (C═O, benzoyl), 162.79 (C═O, amide), 143.68 (C_3), 141.57 (C_5), 143.36, 133.27, 132.70, 131.86, 130.86, 130.51, 130.16, 129.80, 129.40, 129.30, 128.93, 128.37, 128.20, 125.96, 125.32, 124.48 (C_4), 21.54, 17.37 (Ar—CH_3). Anal. Cal. for $C_{31}H_{25}N_3O_5S$ (551,61 g/mol): C, 67.50; H, 4.57; N, 7.62. Found: C, 67.41; H, 4.60; N, 7.68.

*2.2.9. 4-2-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-hydrazinyl- benzene-sulfonic acid (**3f**)*

Compound **3f** was prepared according to the synthesis of **3e**. The yield was 0.36 g (60%), mp 243 °C; IR (ν, cm^{-1}): 3131–3144 (—NH), 3000 (aromatic C—H), 2984 (aliph. C—H), 1669 (C═O, benzoyl), 1669 (HN—C═O), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.08 (b, 2H, —NH), 7.89–6.58 (m, 17H, Ar—H), 5.65 (d, 2H, —NH), 2.2, 1.85 (s, 3H, Ar—CH_3), 1.90 (b, 1H, —OH), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 192.62 (C═O, benzoyl), 164.13 (C═O, amide), 146.13 (C_3), 144.32 (C_5), 141.12, 139.57, 136.41, 134.55, 133.67, 133.36, 132.65, 132.53, 131.77, 131.02, 130.79, 130.63, 130.21, 129.84, 129.46, 129.04, 128.73, 128.54, 128.02, 127.45, 127.20, 121.40, 121.23 (C_4), 20.74, 16.89 (Ar—CH_3), MS (*m*/*z*): Calc. = 566.1, Found = 566.1.

*2.2.10. 1-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-urea (**3g**)*

The yield 0.37 g (80%), mp 199 °C; IR (ν, cm^{-1}): 3421 (b, —NH), 3072 (aromatic C—H), 2846 (aliph. C—H), 1703 (C═O, benzoyl), 1664 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.01 (b, 1H, —NH), 7.83–6.44 (m, 13H, Ar—H), 5.64 (s, 2H, —NH_2), 2.14, 1.76 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.43 (C═O, benzoyl), 162.89 (C═O, amide), 160.47 (C═O, urea), 145.46 (C_3), 144.69 (C_5), 143.28, 142.42, 140.88, 138.14, 137.46, 136.31, 135.49, 133.61, 132.20, 131.60, 129.67, 129.56, 128.58, 128.17, 127.73, 127.04, 126.01, 120.72 (C_4), 19.02, 17.34 (Ar—CH_3). Anal. Cal. for $C_{26}H_{22}N_4O_3$ (438,48 g/mol): C, 71.22; H, 5.06; N, 12.78. Found: C, 71.16; H, 5.04; N, 12.84.

*2.2.11. 1-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-3-methylurea (**3h**)*

(0.33 g, 70%), mp 185 °C; IR (ν, cm^{-1}): 3335–3121 (b, —NH), 3059 (aromatic C—H), 2865 (aliph. C—H), 1668 (C═O, benzoyl), 1668 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.05 (b, 1H, —NH), 7.83–6.44 (m, 13H, Ar—H), 6.31 (q, 1H, —NH), 2.54 (d, 3H, CH_3), 2.02, 1.76 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.08 (C═O, benzoyl), 161.55 (C═O, amide), 160.00 (C═O, urea), 145.95 (C_3), 142.08 (C_5), 141.13, 137.62, 136.97, 133.64, 131.71, 131.12, 131.00, 129.84, 129.60, 129.51, 129.40, 128.60, 128.15, 127.11, 125.31, 121.78 (C_4), 37.60 (N-CH_3), 19.02, 17.34 (Ar—CH_3). Anal. Cal. for $C_{27}H_{24}N_4O_3$ (452,50 g/mol): C, 71.67; H, 5.35; N, 12.38. Found: C, 71.59; H, 5.37; N, 12.45.

*2.2.12. 1-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-3-phenylurea (**3i**)*

(0.38 g, 70%); mp 200 °C; IR (ν, cm^{-1}): 3389–3154 (b, —NH), 3060 (aromatic C—H), 2925 (aliph. C—H), 1670 (C═O, benzoyl), 1670 (C═O, urea), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.64 (C═O, benzoyl), 166.92 (C═O, amide), 165.14 (C═O, urea), 145.71 (C_3), 144.30 (C_5), 138.23, 135.49, 133.44, 132.12, 131.69, 131.29, 130.93, 129.82, 129.37, 129.25, 129.04, 128.68, 128.18, 127.74, 114.21 (C_4), 19.74, 17.11 (Ar—CH_3). Anal. Cal. for $C_{32}H_{26}N_4O_3$ (514,57 g/mol): C, 74.69; H, 5.09; N, 10.89. Found: C, 74.60; H, 5.10; N, 10.93.

*2.2.13. 4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl isothiocyanate (**3j**)*

Compound **5** of 0.199 g (0.5 mmole) was dissolved in 20 mL anhydrous acetone and to a solution of 0.38 g, 0.5 mmole ammonium thiocyanate in dry acetone added the reaction pot. The reaction mixture refluxed four hour in a round-bottom flask equipped with condenser and the solvent was evaporated and residue compound was washed with ether and the formed precipitated product was filtered and the crude product was from n-hexane/ether by crystallization. (0,18 g, 60%), mp 159 °C; IR (ν, cm^{-1}): 3053–3023 (aromatic C—H), 2957 (aliph. C—H), 1698 (C═O, benzoyl), 1670 (C═O), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78–6.97 (m, 13H, Ar—H), 2.09, 1.27 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 190.24 (C═O, benzoyl), 183.01 (C═O), 147.13 (N═C═S), 143.63 (C_3), 141.59 (C_5), 138.03, 137.89, 136.44, 135.80, 134.66, 133.23, 131.14, 131.08, 129.18, 126.11, 114.89, 109.19 (C_4), 19.77, 17.96 (Ar—CH_3). Anal. Cal. for $C_{26}H_{19}N_3O_2S$

(437,51 g/mol): C, 71.38; H, 4.38; N, 9.60. Found: C, 71.29; H, 4.40; N, 9.65.

2.2.14. 1-(4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)thiourea (**3k**)

Compound **3k** can be synthesized in two different methods.

Method A: Compound **2a** of 0.404 g, 1 mmole and 0,038 g, 1 mmole thiourea was refluxed in xylene for 5 h. After evaporation, the oily residue was treated with dry ether, the formed precipitated product was filtered and the crude product was crystallized from ethanol (0.05 g, 21%).

Method B: Compound **3j** of 0.219 g, 0,5 mmole was dissolved in 10 mL anhydrous acetone and drop wise addition of ammonia was heated at reflux temperature for 4 h. After heating to room temperature, stirring was continued 1 h afterward poured into 10 mL cold water, the formed precipitated product was filtered and the crude product was crystallized from ethanol. (0,085 g, 38%), mp 192 °C; IR (ν, cm^{-1}): 3204 (b, —NH), 3057 (aromatic C—H), 2924 (aliph. C—H), 1661 (C═O, benzoyl), 1634 (C═S, thioamide), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 8.19 (b, 1H, —NH), 7.92–6.55 (m, 13H, Ar—H), 2.08, 1.09 (s, 3H, Ar—CH_3), 1.61 (s, 2H, —NH_2), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 189.53 (C═O, benzoyl), 178.61, (C═S, thioamide), 163.72 (C═O, amide), 142.73 (C_3), 141.69 (C_5), 141.36, 137.28, 136.53, 135.63, 134.78, 133.42, 131.23, 131.15, 128.35, 125.92, 113.62 (C_4), 20.24, 17.85 (Ar—CH_3). Anal. Cal. for $C_{26}H_{22}N_4O_2S$ (454,54 g/mol): C, 68.70; H, 4.88; N, 12.33. Found: C, 68.61; H, 4.87; N, 12.39.

2.2.15. 1-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-3-ethylthiourea (**3l**)

Compound **3l** was prepared according to method B. (0.16 g, 44%), mp 201 °C; (was crystallized from propyl alcohol); IR (ν, cm^{-1}): 3196 (—NH), 3049 (aromatic C—H), 2853 (aliph. C—H), 1700 (C═O, benzoyl), 1680 cm^{-1} (C═O, amide), 1666 (C═S, thioamide), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 8.3 (b, 1H, —NH), 7.92–6.72 (m, 13H, Ar—H), 4.1 (q, 2H, CH_2), 2.10, 1.75 (s, 3H, Ar—CH_3), 1.1 (t, 3H, CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 204.29 (C═O, benzoyl), 181.14 (C═S, thioamide), 162.54 (C═O, amide), 143.52 (C_3), 141.62 (C_5), 138.13, 136.18, 135.49, 132.72, 131.50, 130.53, 129.21, 127.19, 125.23, 121.63, 108.13 (C_4), 59.03 (-CH_2), 22.01, 16.92 (Ar—CH_3), 12.35 (CH_3). Anal. Cal. for $C_{28}H_{26}N_4O_2S$ (482,60 g/mol): C, 69.69; H, 5.43; N, 11.61. Found: C, 69.58; H, 5.44; N, 11.72.

2.2.16. 4-Ethyl 3-methyl 1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylate (**3m**)

Compound **3m** was prepared according to the general procedure for synthesis of ester. (0.32 g, 80%), mp 150 °C; (was crystallized from methanol); IR (ν, cm^{-1}): 3064 (aromatic C—H), 2980 (aliph. C—H), 1723 (C═O, ester) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.9–6.8 (m, 8H, Ar—H), 4.2 (q, 2H, —CH_2), 3.7 (s, 3H, —OCH_3) 2.0, 1.7 (s, 3H, Ar—CH_3), 1.1 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.16 (C═O, ester), 161.48 (C═O, ester), 143.35 (C_3), 141.30 (C_5), 138.12, 135.24, 134.56, 131.97, 130.46, 130.05, 129.19, 126.60, 110.33 (C_4), 60.12 (—CH_2), 35.28 (—OCH_3) 23.56, 17.21 (Ar—CH_3), 13.02 (—CH_3). Anal. Cal. for $C_{22}H_{22}N_2O_4$ (378,42 g/mol): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.88; N, 7.51.

2.2.17. Diethyl 1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylate (**3n**)

Compound **3n** was prepared according to the general procedure for synthesis of ester. (0.25 g, 60%), mp 165 °C; (was crystallized from ethanol); IR (ν, cm^{-1}): 3026 (aromatic C—H), 2979 (aliph. C—H), 1721 (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55–6.38 (m, 8H, Ar—H), 4.35 (q, 4H, —CH_2), 2.18, 1.78 (s, 3H, Ar—CH_3), 1.36 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.14, 160.83 (C═O, ester), 143.71 (C_3), 141.64 (C_5), 139.25, 135.47, 134.59, 131.88, 130.63, 129.36, 122.20, 110.33 (C_4), 55.47, 48.91 (O—CH_2), 21.35, 17.29 (Ar—CH_3), 15.34, 13.60 (—CH_3). Anal. Cal. for $C_{23}H_{24}N_2O_4$ (392,45 g/mol): C, 70.39; H, 6.16; N, 7.14. Found: C, 70.33; H, 6.12; N, 7.22.

2.2.18. Ethyl 3-carbamoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**3o**)

Compound **3o** was prepared according to the general procedure for synthesis of amide. (0.32 g, 80%); mp 263 °C; (was crystallized from ethanol); IR (ν, cm^{-1}): 3221 (—NH_2), 3021 (aromatic C—H), 2969 (aliph. C—H), 1735 (C═O, ester), 1725(C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77–7.07 (m, 8H, Ar—H), 4.19 (q, 2H, CH_2), 2.10, 1.76 (s, 3H, Ar—CH_3), 1.22 (t, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.32 (C═O, ester), 166.01 (C═O, amide), 144.42 (C_3), 143.35 (C_5), 138.26, 134.63, 132.12, 131.49, 130.78, 130.04, 129.85, 129.22, 128.52, 127.78, 125.62, 110.25 (C_4), 61.35 (—CH_2), 21.46, 19.03 (Ar—CH_3), 14.15 (—CH_3). Anal. Cal. for $C_{22}H_{24}N_3O_3$ (378,44 g/mol): C, 69.82; H, 6.39; N, 11.10. Found: C, 69.71; H, 6.40; N, 11.19.

2.2.19. Ethyl 1-(2,5-dimethylphenyl)-3-(ethylcarbamoyl)-5-phenyl-1H-pyrazole-4-carboxylate (**3p**)

Compound **3p** was prepared according to the general procedure for synthesis of amide. (0.23 g, 55%), mp 155 °C; (was crystallized from ethanol); IR (ν, cm^{-1}): 3385 (—NH), 3010 (aromatic C—H), 2825 (aliph. C—H), 1715 (C═O, ester), 1616 (C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.12 (b, 1H, NH), 7.70–6.59 (m, 8H, Ar—H), 4.25 (q, 2H, CH_2), 2.01,1.75 (s, 3H, Ar—CH_3), 1,21 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.38 (C═O, ester), 168.41 (C═O, amide), 144.39 (C_3), 142.51 (C_5), 140.86, 135.99, 132.32, 131.29, 130.01, 129.80, 129.68, 129.14 128.52, 127.77, 126.82, 110.25 (C_4), 61.35 (O—CH_2), 35.11 (CH_2—NH), 21.46, 19.03 (Ar—CH_3), 16.51, 14.68 (—CH_3). Anal. Cal. for $C_{23}H_{25}N_3O_3$ (391,46 g/mol): C, 70.57; H, 6.44; N, 10.73. Found: C, 70.48; H, 6.45; N, 10.80.

2.2.20. Ethyl 1-(2,5-dimethylphenyl)-5-phenyl-3-(phenylcarbamoyl)-1H-pyrazole-4-carboxylate (**3r**)

Compound **3r** was prepared according to the general procedure for synthesis of amide. (0.24 g, 50%), mp 205 °C; (was crystallized from isoamylalcohol/secondary butyl alcohol); IR (ν, cm^{-1}): 3219 (—NH), 3045 (aromatic C—H), 2923 (aliph. C—H), 1732 (C═O, ester), 1633 (C═O, amide), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.41 (C═O, ester), 162.56 (C═O, amide), 145.34 (C_3), 144.14 (C_5), 136.14, 135.63,

133.38, 132.40, 131.16, 130.73, 129.90, 129.51 129.28, 129.06, 128.58, 128.26, 127.43, 114.30 (C_4), 50.31 (O—CH_2), 20.48, 17.35 (Ar—CH_3), 12.10 (—CH_3). Anal. Cal. for $C_{27}H_{25}N_3O_3$ (439,51 g/mol): C, 73.78; H, 8.78; N, 9.56. Found: C, 73.67; H, 8.75; N, 10.09.

*2.2.21. Ethyl 1-(2,5-dimethylphenyl)-5-phenyl-3-(ureidocarbonyl)-1H-pyrazole-4-carboxylate (**3s**)*

Compound **3s** was prepared according to the general procedure for synthesis of urea. (0.33 g, 75%); mp 228 °C, (was crystallized from isoamylalcohol); IR (ν, cm^{-1}): 3408–3157 (b, N—H), 3054 (aromatic C—H), 2923 (aliph. C—H), 1732 (C═O, ester), 1690 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (b, 1H, —NH), 7.78–6.90 (m, 8H, Ar—H), 5.54 (s, 2H, —NH_2), 4.20 (q, 3H, CH_2), 1.95, 1.69 (s, 3H, Ar—CH_3), 1.29 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.19 (C═O, ester), 162.03 (C═O, amide), 158.54 (C═O, urea), 143.66 (C_3), 142.27 (C_5), 140.35, 135.57, 134.20, 130.79, 130.38, 129.54, 122.41, 107.54 (C_4), 51.80 (—CH_2), 22.48, 17.25 (Ar—CH_3), 14.66 (CH_3). Anal. Cal. for $C_{22}H_{22}N_4O_4$ (406,43 g/mol): C, 65.01; H, 5.46; N, 13.78. Found: C, 64.87; H, 5.49; N, 13.87.

*2.2.22. Ethyl 1-(2,5-dimethylphenyl)-3-((3-methylureido)-carbonyl)-5-phenyl-1H-pyrazole-4-carboxylate (**3t**)*

Compound **3t** was prepared according to the general procedure for synthesis of urea. (0.32 g, 70%); mp 262 °C, (was crystallized from secondary butyl alcohol); IR (ν, cm^{-1}): 3401–3157 (b, N—H), 3014 (aromatic C—H), 2916 (aliph. C—H), 1702 (C═O, ester), 1700 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (b, 1H, —NH), 7.37–6.56 (m, 8H, Ar—H), 5.44 (s, 1H, —NH), 4.19 (q, 2H, CH_2), 3.49 (t, 3H, CH_3), 2.06, 1.78 (s, 3H, Ar—CH_3), 1,18 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.55 (C═O, ester), 166.72 (C═O, amide), 161.49 (C═O, urea), 145.27 (C_3), 143.64 (C_5), 141.12, 136.13, 132.29, 131.44, 130.57, 130.23, 129.67, 128.36, 125.37, 106.10 (C_4), 58.82 (O—CH_2), 31.19 (CH_3—NH), 24.28, 18.10 (Ar—CH_3), 15.36 (CH_3). Anal. Cal. for $C_{23}H_{24}N_4O_4$ (420,46 g/mol): C, 65.70; H, 5.75; N, 13.33. Found: C, 65.59; H, 5.77; N, 13.41.

*2.2.23. Ethyl 1-(2,5-dimethylphenyl)-3-((3-ethylureido)-carbonyl)-5-phenyl-1H-pyrazole-4 carboxylate (**3u**)*

Compound **3u** was prepared according to the general procedure for synthesis of urea. (0.24 g, 50%), mp 220 °C; (was crystallized from chloroform/n-hexane); IR (ν, cm^{-1}): 3367–3100 (b, N—H), 3055 (aromatic C—H), 2928 (aliph. C—H), 1722 (C═O, ester), 1722 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (b, 1H, —NH), 7.70–6.79 (m, 8H, Ar—H), 5.39 (s, 1H, —NH), 4.58 (q, 2H, CH_2), 3.45 (q, 3H, CH_2), 2.10, 1.84 (s, 3H, Ar—CH_3), 1.46 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.38 (C═O, ester), 163.15 (C═O, amide), 161.74 (C═O, urea), 143.31 (C_3), 142.64 (C_5), 141.25, 137.48, 135.56, 133.39, 131.36, 130.63, 130.19, 129.83, 129.25, 128.91, 128.42, 125.54, 108.42 (C_4), 56.44 (O—CH_2), 34.65 (CH_2—NH), 22.17, 19.25 (Ar—CH_3), 15.48, 12.06 (—CH_3). Anal. Cal. for $C_{24}H_{26}N_4O_4$ (434,49 g/mol): C, 66.34; H, 6.03; N, 12.89. Found: C, 66.25; H, 6.05; N, 12.95.

2.2.24. General procedure for synthesis of pyrazolo[3,4-d] pyridazine

A miliequimolar mixture of **1a,b** and appropriate hydrazine was refluxed in xylene for 24 h. After the solvent was removed by evaporation, the oily residue was treated with ether and the formed crude product was crystallized from appropriate solvent.

*2.2.25. 2-(2,5-Dimethylphenyl)-3,4,6-triphenyl-2H-pyrazolo [3,4-d]pyridazin-7(6H)-one (**4a**)*

(0.227 g, 45%), mp 224 °C; (was crystallized from hexane); IR (ν, cm^{-1}): 3056 (aromatic C—H), 2920 (aliph. C—H), 1696 (C_7),1650 (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89–6.61 (m, 18H, Ar—H), 2.23,1.82 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.40 (C_7), 145.51 (C-7a), 144.36 (C_3), 143.33 (C_4), 140.84, 139.20, 138.38, 136.30, 133.81, 132.95, 131.35, 130.64, 129.69, 129.12, 128.68, 128.54, 128.12, 127.43, 126.76, 112.15 (C-3a), 18.76, 17.33 (Ar—CH_3). Anal. Cal. for $C_{31}H_{24}N_4O$ (468,55 g/mol): C, 79.46; H, 5.16; N, 11.96. Found: C, 79.39; H, 5.15; N, 12.04.

2.2.25.1. 2-(2,5-Dimethylphenyl)-3,4-diphenyl-2H-pyrazolo [3,4-d]pyridazin-7(6H)-one (4b). (0.16 g, 36%), mp 262 °C; (was crystallized from xylene/methanol); IR (ν, cm^{-1}): 3421 (—NH), 3055 (aromatic C—H), 2985 (aliph. C—H), 1658 (C_7), 1638 (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.11 (s, 1H, —NH), 7.28–6.58 (m, 13H, Ar—H), 2.23, 1.82 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 160.67 (C_7), 145.55 (C-7a), 144.41 (C_3), 143.32 (C_4), 140.21, 138.45, 136.78, 134.64, 133.13, 132.62, 130.23, 129.97, 129.65, 128.60, 128.15, 127.77, 127.32, 126.64, 110.72 (C-3a), 20.46, 17.31 (Ar—CH_3). Anal. Cal. for $C_{25}H_{20}N_4O$ (392,45 g/mol): C, 76.51; H, 5.14; N, 14.28. Found: C, 76.43; H, 5.12; N, 14.33.

*2.2.25.2. 2,6-Bis(2,5-dimethylphenyl)-3,4-diphenyl-2H-pyrazolo [3,4-d]pyridazin-7(6H)-one (**4c**).* (0.14 g, 25%), mp 194 °C; (was crystallized from xylene); IR (ν, cm^{-1}): 3057 (aromatic C—H), 2901 (aliph. C—H), 1664 (C_7), 1632 (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79–7.08 (m, 16H, Ar—H), 2.28, 2.07 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.73 (C_7), 146.18 (C-7a), 145.32 (C_3), 144.38 (C_4), 143.32, 143.07, 142.86, 139.63, 139.44, 139.11, 134.20, 133.44, 132.71, 132.31, 130.51, 130.42, 129.95, 129.33, 128.93, 128.51, 127.63, 127.20, 126.81, 124.51, 122.26, 110.05 (C-3a), 21.51, 17.33 (Ar—CH_3). Anal. Cal. for $C_{33}H_{28}N_4O$ (496,60 g/mol): C, 79.81; H, 5.68; N, 11.28. Found: C, 79.71; H, 5.69; N, 11.37.

*2.2.25.3. 2-(2,5-Dimethylphenyl)-6-(3,4-dimethylphenyl)-3,4-diphenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4d**).* (0.17 g, 30%), mp 187 °C; (was crystallized from xylene); IR (ν, cm^{-1}): 3041 (aromatic C—H), 2914 (aliph. C—H), 1675 (C_7), 1600 (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.94–7.41 (m, 16H, Ar—H), 2.40, 2.07 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.03 (C_7), 145.93 (C-7a), 144.53 (C_3), 143.23 (C_4), 139.87, 139.10, 138.83, 138.72, 129.38, 129.12, 128.42, 128.12, 127.94, 127.41, 127.12, 126.33, 126.10, 124.35, 111.42 (C-3a), 20.45, 17.81 (Ar—CH_3). Anal. Cal. for $C_{33}H_{28}N_4O$ (496,60 g/mol): C, 79.81; H, 5.68; N, 11.28. Found: C, 79.69; H, 5.69; N, 11.38.

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008

*2.2.25.4. 2-(2,5-Dimethylphenyl)-6-(2,4-dinitrophenyl)-3,4-diphenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4e**).* (0.24 g, 40%), mp 210 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3059 (aromatic C—H), 2925 (aliph. C—H), 1649 (C_7), ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 163.43 (C_7), 145.66 (C-7a), 144.39 (C_4), 141.35 (C_3), 138.47, 136.73, 135.45, 133.30, 130.27, 129.94, 128.70, 128.54, 128.12, 127.28, 127.14, 125.12, 111.42 (C-3a), 20.45, 17.81 (Ar—CH_3). Anal. Cal. for $C_{31}H_{22}N_6O_5$ (558,54 g/mol): C, 66.66; H, 3.97; N, 15.05. Found: C, 66.55; H, 3.95; N, 15.17.

*2.2.25.5. 2-(2,5-Dimethylphenyl)-3,4-diphenyl-6-(2,4,6-trichlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4f**).* (0.213 g, 37%), mp 217 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3060 (aromatic C—H), 2925 (aliph. C—H), 1670 (C_7), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.56 (C_7), 145.47 (C-7a), 142.24 (C_3), 137.81 (C_4), 136.73, 133.84, 132.62, 131.52, 131.00, 129.83, 129.48, 129.39, 129.26, 129.14, 128.71, 128.25, 127.35, 125.47, 121.62, 108.51 (C-3a), 19.35, 17.12 (Ar—CH_3). Anal. Cal. for $C_{31}H_{21}N_4OCl$ (571,88 g/mol): C, 65.11; H, 3.70; N, 9.80. Found: C, 65.03; H, 3.71; N, 9.85.

*2.2.25.6. 2-(2,5-Dimethylphenyl)-3,4-diphenyl-6-(4-(trifluoromethyl)phenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4g**).* (0.26 g, 45%), mp 219 °C; (was crystallized from ether/hexane); IR (ν, cm^{-1}): 3080 (aromatic C—H), 2840 (aliph. C–H), 1673 (C_7), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.45 (C_7), 144.34 (C-7a), 143.81 (C_3), 142.54 (C_4), 141.47, 138.39, 136.56, 135.63, 133.72, 132.16, 130.90, 130.75, 129.82, 129.73, 129.44, 129.20, 129.04, 128.61, 127.76, 127.32, 121.85, 108.41 (C-3a), 20.39, 17.41 (Ar—CH_3). Anal. Cal. for $C_{23}H_{23}N_4OF_3$ (536,55 g/mol): C, 71.63; H, 4.32; N, 10.44. Found: C, 71.56; H, 4.33; N, 10.51.

*2.2.25.7. 2-(2,5-Dimethylphenyl)-4-ethoxy-3,6-diphenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4h**).* (0.23 g, 50%), mp 205 °C; (was crystallized from toluene); IR (ν, cm^{-1}): 3090 (aromatic C—H), 2980 (aliph. C—H), 1722 (C_7), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74–6.43 (m, 13H, Ar—H), 3.79 (q, 2H, —CH_2), 2.07, 1.81 (s, 3H, Ar—CH_3), 1.76 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.72 (C_7), 147.68 (C_4), 144.32 (C-7a), 142.12 (C_3), 135.45, 134.59, 133.30, 132.35, 131.27, 130.12, 129.63, 129.07, 128.54, 127.31, 126.18, 118.32 (C-3a), 61.28 (—CH_2), 21.47, 17.47 (Ar—CH_3), 14.36 (-CH_3). Anal. Cal. for $C_{27}H_{24}N_4O_2$ (436,51 g/mol): C, 74.29; H, 5.54; N, 12.84. Found: C, 74.20; H, 5.55; N, 12.91.

*2.2.25.8. 2-(2,5-Dimethylphenyl)-4-ethoxy-3-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4i**).* (0.27 g, 65%), mp 140 °C; (was crystallized from toluene); IR (ν, cm^{-1}): 3026 (aromatic C—H), 2946 (aliph. C—H), 1645 (C_7), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96–7.29 (m, 8H, Ar—H), 5.11 (s, 1H, —NH), 3.51 (q, 2H, —CH_2), 1.82, 1.47 (s, 3H, Ar—CH_3), 1.22 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.52 (C_7), 144.20 (C_4), 142.74 (C-7a), 142.15 (C_3), 141.51, 136.63, 134.28, 132.45, 131.52, 130.39, 129.64, 129.06, 128.31, 127.44, 126.36 (C-3a), 60.35 (O—CH_2), 22.64, 17.85 (Ar—CH_3), 14.25 (—CH_3). Anal. Cal. for $C_{21}H_{20}N_4O_2$ (360,41 g/mol): C, 69.98; H, 5.59; N, 15.55. Found: C, 69.90; H, 5.60; N, 15.63.

*2.2.25.9. 2,6-bis(2,5-Dimethylphenyl)-4-ethoxy-3-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4j**).* (0.15 g, 30%); mp 190 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3061 (aromatic C—H), 2979 (aliph. C—H), 1713 (C_7), 1633 cm^{-1} (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.7–6.4 (m, 11H, Ar—H), 4.2 (q, 2H, —CH_2), 2.5, 1.5 (s, 3H, Ar—CH_3), 1.1 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.27 (C_7), 146.38 (C_4), 144.12 (C-7a), 139.25 (C_3), 137.10, 129.64, 129.56, 129.48, 129.26, 128.74, 128.61, 128.43, 128.32, 128.15, 110.71 (C-3a), 61.45 (—CH_2), 21.35, 17.28 (Ar—CH_3) 13.56 (—CH_3). Anal. Cal. for $C_{29}H_{28}N_4O_2$ (464,56 g/mol): C, 74.98; H, 6.08; N, 12.06. Found: C, 74.85; H, 6.09; N, 12.15.

*2.2.25.10. 2-(2,5-Dimethylphenyl)-6-(3,4-dimethylphenyl)-4-ethoxy-3-phenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4k**).* (0.15 g, 30%), mp 220 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3020 (aromatic C—H), 2975 (aliph. C—H), 1724 (C_7), 1633 cm^{-1} (C_4), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.7–6.5 (m, 11H, Ar—H), 4.1 (q, 2H, —CH_2), 2.3, 1.6 (s, 3H, Ar—CH_3), 1.1 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.11 (C_7), 145.14 (C_4), 144.39 (C-7a), 136.09 (C_3), 136.45, 135.49, 132.20, 130.44, 129.96, 129.48, 129.12, 128.39, 128.26, 126.32, 114.18 (C-3a), 61.20 (—CH_2), 18.74, 17.21 (Ar—CH_3), 14.14 (—CH_3). Anal. Cal. for $C_{29}H_{28}N_4O_2$ (464,56 g/mol): C, 74.98; H, 6.08; N, 12.06. Found: C, 74.89; H, 6.07; N, 12.14.

*2.2.25.11. 2-(2,5-Dimethylphenyl)-6-(2,4-dinitrophenyl)-4-ethoxy-3-phenyl2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4l**).* (0.25 g, 45%), mp 194 °C; (was crystallized from chloroform/n-hexane); IR (ν, cm^{-1}): 3088 (aromatic C—H), 2925 (aliph. C—H), 1631 (C_7), 1615 (C_4), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 161.95 (C_7), 145.76 (C_4), 144.53 (C-7a), 143.71 (C_3), 136.40, 136.18, 135.32, 134.36, 133.38, 132.60, 131.22, 130.85, 130.66, 129.72, 129.61, 129.30, 129.11, 128.86, 128.68, 128.17, 127.19, 125.62, 114.25 (C-3a), 50.14 (O—CH_2), 20.62, 17.20 (Ar—CH_3), 13.86, (—CH_3). Anal. Cal. for $C_{27}H_{22}N_6O_6$ (526,50 g/mol): C, 61.59; H, 4.21; N, 15.96. Found: C, 61.51; H, 4.18; N, 16.09.

*2.2.25.12. 2-(2,5-Dimethylphenyl)-4-ethoxy-3-phenyl-6-(2,4,6-trichlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4m**).* (0.19 g, 40%), mp 170 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3026 (aromatic C—H), 2956 (aliph. C—H), 1684 (C_7), 1634 cm^{-1} (C_4), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.43 (C_7), 144.53 (C_4), 143.72 (C-7a), 142.64 (C_3), 141.44, 139.63, 136.71, 135.53, 133.72, 132.10, 130.75, 130.43, 129.91, 129.63, 129.54, 129.30, 128.87, 128.69, 126.84, 121.44 (C-3a), 49.74 (O-CH_2), 19.35, 17.43 (Ar—CH_3), 14.02 (—CH_3). Anal. Cal. for $C_{27}H_{21}N_4O_2Cl_3$ (539,84 g/mol): C, 60.07; H, 3.92; N, 10.38. Found: C, 59.96; H, 3.93; N, 10.51.

*2.2.25.13. 2-(2,5-Dimethylphenyl)-4-ethoxy-3-phenyl-6-(4-(trifluoromethyl)phenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**4n**).* (0.22 g, 40%), mp 158 °C; (was crystallized from chloroform/hexane); IR (ν, cm^{-1}): 3040 (aromatic C—H), 2950 (aliph. C—H), 1723 (C_7), 1615 cm^{-1} (C_4), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.84 (C_7), 146.38 (C_4), 144.35 (C-7a), 143.19 (C_3), 140.76, 139.34, 137.43, 135.58, 133.31, 132.56, 131.69, 129.74, 129.40, 129.29, 129.12, 128.73, 128.45,

128.22, 127.67, 126.84, 120.72 (C-3a), 50.43 (O—CH_2), 19.58, 17.24 (Ar—CH_3), 13.40 (—CH_3). Anal. Cal. for $C_{28}H_{23}N_4O_2F_3$ (504,50 g/mol): C, 66.66; H, 4.60; N, 11.11. Found: C, 66.57; H, 4.62; N, 11.19.

*2.2.25.14. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid (**5**).* Compound **1b** 0.364 g (1 mmole) was refluxed in solution of 0.1 g (2.5 mmole) NaOH for about 1.5 h. Mixed solution was cooled down to room temperature. It was stirred for a while by adding 1.5 mL concentrated HCl and water at equal volume. Precipitated white solid product was filtered and washed with water again. It was crystallized from butanol (0,384 g, 85%), mp 100 °C; IR (ν, cm^{-1}): 3392 (b, —OH), 3058–3022 (aromatic C—H), 2976 (aliph. C—H), 1716–1683 (C═O, acide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.37, 9.88 (b, 1H, —OH), 7.80–7.09 (m, 8H, Ar—H), 2.30, 1.74 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.78, 164.57 C═O, acide, 145.03 (C_3), 143.06 (C_5), 133.72, 131.17, 130.86, 130.61, 129.77, 129.53, 129.13, 128.94, 128.41, 127.73, 127.66, 127.14, 110.26 (C_4), 27.18, 19.21 (Ar—CH_3). Anal. Cal. for $C_{19}H_{16}N_2O_4$ (336,34 g/mol): C, 67.85; H, 4.79; N, 8.33. Found: C, 67.79; H, 4.78; N, 8.41.

*2.2.26. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarbonyl dichloride (**6**)*

Compound **6** was prepared according to the general procedure for synthesis of acylchlorur. (0.4 g, 68%), mp 98 °C; (was crystallized from chloroform/n-hexane); IR (ν, cm^{-1}): 3058 (aromatic C—H), 2969 (aliph. C—H), 1716, 1683 (C═O, acyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19–7.11 (m, 8H, Ar—H), 2.22, 1.82 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.00, 163.00 (C═O, acyl), 142.45 (C_3), 141.81 (C_5), 133.32, 131.34, 130.99, 130.16, 129.89, 129.56, 129.16, 128.66, 128.26, 126.88, 108.65 (C_4), 23.30, 17.26 (Ar—CH_3), MS (*m*/*z*): Calc. = 372.0, Found = 372.1.

*2.2.27. Dimethyl 1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylate (**7a**)*

Compound **7a** was prepared according to the general procedure for synthesis of ester. (0.35 g, 84%), mp 140 °C; (was crystallized from methanol); IR (ν, cm^{-1}): 3026 (aromatic C—H), 2951 (aliph. C—H), 1724 (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90–6.59 (m, 8H, Ar—H), 3.66 (s, 3H, CH_3), 2.04, 1.84 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.50, 163.46 (C═O, ester), 145.18 (C_3), 143.73 (C_5), 140.41, 138.26, 136.35, 132.80, 131.67, 130.52, 129.15, 128.33, 124.64, 110.55 (C_4), 47.50 (CH_3), 21.51, 17.49 (Ar—CH_3). Anal. Cal. for $C_{21}H_{20}N_2O_4$ (364,39 g/mol): C, 69.22; H, 5.53; N, 7.69. Found: C, 69.16; H, 5.54; N, 7.75.

*2.2.28. Diethyl 1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylate (**7b**)*

Compound **7b** was prepared according to the general procedure for synthesis of ester. (0.324 g, 73%), mp 118 °C; (was crystallized from ethanol); IR (ν, cm^{-1}):3060–3022 (aromatic C—H), 2979–2919 (aliph. C—H), 1717 (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42–6.39 (m, 8H, Ar—H), 4.43 (q, 2H, CH_2), 2.22, 1.81 (s, 3H, Ar—CH_3), 1.44 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.22, 159.67 (C═O, ester), 143.71 (C_3), 141.40 (C_5), 139.21, 135.39, 134.55, 131.62, 130.71, 130.08, 129.47, 128.21, 112.32 (C_4), 49.15, 44.34 (CH_2), 19.28, 17.41 (Ar—CH_3), 12.53, 11.70 (CH_3). Anal. Cal. for $C_{23}H_{24}N_2O_4$ (392,45 g/mol): C, 70.39; H, 6.16; N, 7.14. Found: C, 70.32; H, 6.18; N, 7.22.

*2.2.29. N^3,N^4-Dicarbamoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxyamide (**7c**)*

Compound **7c** was prepared according to the general procedure for synthesis of urea. (0.3 g, 59%), mp 240 °C; (was crystallized from ether/n-hexane); IR (ν, cm^{-1}): 3407–3153 (b, N—H), 3056 (aromatic C—H), 2946 (aliph. C—H), 1646 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.38 (b, 1H, NH), 7.84–6.49 (m, 8H, Ar—H), 5.68, 5.40 (s, 2H, —NH_2), 2.23, 1.85 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.04, 164.77 (C═O, amide), 164.43, 160.35 (C═O, urea), 148.84 (C_3), 146.49 (C_5), 143.11, 141.31, 136.46, 135.00, 134.57, 133.97, 133.33, 130.81, 129.69, 128.86, 127.56, 114.02 (C_4), 24.81, 17.23 (Ar—CH_3). Anal. Cal. for $C_{21}H_{20}N_6O_4$ (420,42 g/mol): C, 59.99; H, 4.79; N, 19.99. Found: C, 59.89; H, 4.76; N, 20.09.

*2.2.30. N^3,N^4-Methyl(carbamoyl)1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxyamide (**7d**)*

Compound **7d** was prepared according to the general procedure for synthesis of urea. (0.35 g, 65%), mp 258 °C; (was crystallized from ether/n-hexane); IR (ν, cm^{-1}): 3336 (b, N—H), 3040 (aromatic C—H), 2822 (aliph. C—H), 1694 (C═O, urea), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.18, 8.95 (b, 1H, NH), 7.86–6.91 (m, 8H, Ar═H), 6.19, 5.84 (q, 1H, ═NH), 2.61 (d, 3H, CH_3), 2.08, 1.73 (s, 3H, Ar═CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.41, 163.26 (C═O, amide), 161.54, 157.39 (C═O, urea), 145.62 (C_3), 141.16 (C_5), 140.03, 136.72, 134.40, 133.36, 132.91, 131.16, 130.23, 129.48, 128.36, 127.52, 126.74, 109.45 (C_4), 36.70 (CH_3), 24.81, 17.23 (Ar—CH_3). Anal. Cal. for $C_{23}H_{24}N_6O_4$ (448,47 g/mol): C, 61.60; H, 5.39; N, 18.74. Found: C, 61.53; H, 5.40; N, 18.81.

*2.2.31. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxyamide (**7e**)*

Compound **7e** was prepared according to the general procedure for synthesis of amide. (0.3 g, 70%), mp 228 °C; (was crystallized from methanol); IR (ν, cm^{-1}): 3446–3152 (b, —NH_2), 3055 (aromatic C—H), 2923 (aliph. C—H), 1672 (C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.79–6.61 (m, 8H, Ar—H), 5.23, 5.12 (s, 2H, —NH_2), 2.23, 1.82 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.19, 163.84 (C═O, amide), 145.62 (C_3), 141.25 (C_5), 133.34, 131.45, 130.91, 129.95, 129.72, 128.86, 128.58, 128.26, 126.61, 113.18 (C_4), 21.14,18.90 (Ar—CH_3). Anal. Cal. for $C_{19}H_{18}N_4O_2$ (334,37 g/mol): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.19; H, 5.44; N, 16.83.

*2.2.32. 1-(2,5-Dimethylphenyl)- N^3,N^4-diethyl-5-phenyl-1H-pyrazole-3,4-dicarboxyamide (**7f**)*

Compound **7f** was prepared according to the general procedure for synthesis of amide. (0.33 g, 69%), mp 182 °C; (was crystallized from n-hexane/chloroform); IR (ν, cm^{-1}): 3396 (b, N—H), 3030 (aromatic C—H), 2979 (aliph. C—H), 1640 (C═O, amide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.65, 9.89 (t, 1H, NH), 7.99–6.85 (m, 8H, Ar—H), 3.75 (q, 2H,

CH_2), 2.2, 1.8 (s, 3H, Ar—CH_3), 1.5 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 164.18, 161.35 (C═O, amide), 144.20 (C_3), 141.52 (C_5), 133.74, 130.45, 129.63, 129.24, 128.76, 128.52, 128.43, 128.22, 128.10, 113.18 (C_4), 51.50 (CH_2), 20.42,17.30 (Ar—CH_3), 14.12, 12.68 (CH_3). Anal. Cal. for $C_{23}H_{26}N_4O_2$ (390,48 g/mol): C, 70.75; H, 6.71; N, 14.35. Found: C, 70.68; H, 6.73; N, 14.43.

*2.2.33. 1-(2,5-Dimethylphenyl)-N³,N⁴,5-triphenyl-1H-pyrazole-3,4-dicarboxyamide (**7g**)*

Compound **7g** was prepared according to the general procedure for synthesis of amide. (0.2 g, 35%), mp 211 °C; (was crystallized from n-hexane/chloroform); IR (ν, cm^{-1}): 3345 (b, N—H), 3040 (aromatic C—H), 2807 (aliph. C—H), 1652 (C═O, amide), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.59, 162.65 (C═O, amide), 144.74 (C_3), 144.39 (C_5), 134.13, 133.36, 132.40, 130.73, 130.24, 129.51, 129.31, 129.06, 128.58, 128.14, 127.63, 112.45 (C_4), 18.24, 17.38 (Ar—CH_3). Anal. Cal. for $C_{31}H_{26}N_4O_2$ (486,56 g/mol): C, 76.52; H, 5.39; N, 11.51. Found: C, 76.41; H, 5.41; N, 11.59.

*2.2.34. 4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonitrile (**8a**)*

A cold solution of the acid amide **3c** (0.421 g, 1 mmole) in a mixture of DMF (0.7 mL) and $SOCl_2$ (0.15 mL) was stirred at 0–5 °C for 2 h. After heating to room temperature, stirring was continued overnight, then the reaction mixture was poured over crushed ice and the separated solid isolated by filtration, washed with water and crystallized from toluene to give 0.417 g (68%) of **8a**, mp 112 °C; IR (ν, cm^{-1}): 3046 (aromatic C—H), 2921 (aliph. C—H), 2165 (—CN,), 1652 cm^{-1} (C═O, benzoyl), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 188.68 (C═O, benzoyl), 146.30 (C_3), 145.13 (C_5), 143.36, 139.12, 136.26, 134.46, 133.85, 130.38, 130.10, 129.83, 129.54, 129.46, 129.24, 128.74, 128.38, 127.10, 126.74, 122.21 (C_4), 116.32 (C≡N), 21.70, 17.37 (Ar—CH_3). Anal. Cal. for $C_{25}H_{19}N_3O$ (377,44 g/mol): C, 79.55; H, 5.07; N, 11.13. Found: C, 79.48; H, 5.09; N, 11.20.

*2.2.35. Ethyl 3-cyano-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**8b**)*

Compound **8b** was prepared according to the general procedure for synthesis of nitrile. (0.30 g, 24%), mp 158 °C; (was crystallized from isoamylalcohol/secondary butyl alcohol); IR (ν, cm^{-1}): 3050 (aromatic C—H), 2924 (aliph. C—H), 2162 cm^{-1} (C≡N, nitrile), 1717 cm^{-1} (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68–6.74 (m, 8H, Ar—H), 4.18 (q, 2H, CH_2), 2.13, 1.79 (s, 3H, Ar—CH_3), 1.18 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.38 (C═O, ester), 147.10 (C_3), 146.55 (C_5), 136.85, 133.72, 130.38, 130.10, 129.74, 129.54, 129.46, 129.24 129.10, 128.83, 128.24, 116.95 (C≡N, nitrile), 107.75 (C_4), 54.84 (CH_2), 21.12, 18.77 (Ar—CH_3), 14.13 (CH_3). Anal. Cal. for $C_{21}H_{19}N_3O_2$ (345,39 g/mol): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.96; H, 5.53; N, 12.26.

*2.2.36. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-dicarbonitrile (**8c**)*

Compound **7e** of 0.334 g (1 mmole) was dissolved in xylene. 5 mL DMF and 0.292 mL (4 mmole) $SOCl_2$ was added in 0 °C. After stirring for 12 h in room temperature, some ice water was added to the mixture. Precipitated solid product was filtered and purified from ethanol–water mixture by crystallization. (0.3 g, 30%), mp 217 °C; IR (ν, cm^{-1}): 3060 (aromatic C–H), 2923 (aliph. C—H), 2207, 2179 (C≡N, nitrile), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07–7.03 (m, 8H, Ar—H), 2.37, 2.13 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.25 (C_3), 144.06 (C_5), 142.92, 135.69, 133.32, 130.93, 129.98, 129.50, 128.56, 126.80, 125.74, 118.17, 116.12 (C≡N), 110.40 (C_4), 18.60, 17.36 (Ar—CH_3), MS (*m*/*z*): Calc. = 298.1, Found = 298.1.

*2.2.37. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazol-4-yl-(phenyl)methanone (**9a**)*

Compound **1a** (0.397 g, 1 mmole) was heated to 210–220 °C in an oil bath for about 30 min without any solvent. After cooling to room temperature, the residue was treated with ether to give the crude product, which was crystallized from n-hexane, to yield 0.32 g (80%); mp 175 °C; IR (ν, cm^{-1}): 3040 (aromatic C—H), 2921 (aliph. C—H), 1649 (C═O, benzoyl), ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 192.32 (C═O, benzoyl), 145.25 (C_3), 144.06(C_5), 142.92, 132.32, 131.16, 130.93, 130.12, 129.93, 129.04, 128.95, 128.84, 128.46, 128.25, 128.03, 127.60, 126.74, 120.11 (C_4), 23.24, 18.04 (Ar—CH_3). Anal. Cal. for $C_{24}H_{20}N_2O$ (352,43 g/mol): C, 81.79; H, 5.72; N, 7.95. Found: C, 81.71; H, 5.74; N, 8.04.

*2.2.38. Ethyl 1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**9b**)*

Compound **1b** (0.364 g, 1 mmole) was heated to 210–220 °C in an oil bath for about 30 min without any solvent. After cooling to room temperature, the residue was treated with ether to give the crude product, which was crystallized from ethanol, to yield 0.27 g (75%), mp 145 °C; IR (ν, cm^{-1}): 3025 (aromatic C—H), 2918 (aliph. C—H), 1723 (C═O, ester), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87–7.11 (m, 8H, Ar—H), 3.82 (q, 2H, —CH_2), 2,19, 1.75 (s, 3H, Ar—CH_3), 1.41 (t, 3H, —CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.56 (C═O, ester), 144.19 (C_3), 142.51 (C_5),141.63, 136.66, 136.23, 133.70, 133.64, 131.29, 130.93, 129.60, 129.20, 128.31, 127.56, 125.28, 113.21 (C_4), 59.70 (—CH_2), 21.98, 18.15 (Ar—CH_3), 14.22 (—CH_3). Anal. Cal. for $C_{20}H_{20}N_2O_2$ (320,38 g/mol): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.89; H, 6.31; N, 8.81.

*2.2.39. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-4-carboxylic acid (**9c**)*

Compound **9c** can be synthesized in two different methods.

Method A: Compound **5** of 0.336 g (1 mmole) was heated at 200 °C until carbon dioxide gas exiting finished. The residue solid was washed with ether and mixed 2 h in room temperature from n-hexane/ether by crystallization (0.25 g, 71%).

Method B: Compound **9a** of 0.320 g (1 mmole) was refluxed in a solution of 0.1 g (2.5 mmole) NaOH for about 2 h. Mixed solution was cooled down to room temperature. It was stirred for a while by adding 1.5 mL concentrated HCl and water at equal volume. Precipitated solid product was filtered and washed with water again. It was crystallized from n-hexane/ether. (0,28 g, 80%), mp 207 °C; IR (ν, cm^{-1}): 3390 (b, —OH), 3057 (aromatic C—H), 2974 (aliph. C—H), 1732

(C═O, acide), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 13.75 (b, 1H, ─OH), 8.18–6.35 (m, 9H, Ar─H), 2.27, 1.80 (s, 3H, Ar─CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 165.73 (C═O, acide), 144.21 (C_3), 143.55 (C_5), 141.55, 141.47, 138.54, 136.34, 131.72, 130.62, 129.48, 129.36, 127.45, 126.63, 122.52 (C_4), 21.63, 17.58 (Ar─CH_3).

*2.2.40. 1-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazol-3-yl)-3-(2-hydroxy-4-methyl-phenyl)-propane-1,3-dione (**10**)*

Compound **2a** of 0.403 g (1 mmole) was dissolved in pyridine (5 mL), the 2-hydroxy-4-methyl-acethophenone 0.150 g (1 mmole) was added and refluxed for 2 h. KOH (0.56 g, 10 mmole) was added to the reaction pot and refluxed for 2 h. During the second period of refluxing, the product was precipitated. After finishing the reaction, 3 M HCl 20 (mL) was added to the cooled solution for neutralizing. The formed precipitated product was filtered and the crude product was from n-hexane/chloroform by crystallization. (0.46 g, 70%), mp 184 °C; IR (ν, cm^{-1}): 3229 cm^{-1} (phenolic ─OH), 3060 (aromatic C─H), 2929 (aliph. C─H), 1709 (C═O), 1637 (C═O, benzoyl), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 8.8 (br, enolform, ─OH) 8.2–6.5 (m, Ar─H), 6.3 (enolform, C═CH), 5.5 (br, Ph─OH), 3.5 (s, ketoform ─CH_2), 2.1, 1.7 (s, Ar─CH_3), 1.2 (Ph─CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 205.1, 195.0, 193.2 (C═O), 161.1, 145.6 (C_3), 144.3 (C_5), 139.8, 136.6, 135.2, 134.2, 133.1, 132.7, 131.2, 130.8, 130.1, 129.9, 129.2, 128.7, 118.2, 109.0 (C_4), 92.8 (enolform, ═CH─), 45.1 (ketoform, CH_2), 27.0 (Ph─CH_3), 20.0, 17.0 (Ar─CH_3), MS (*m*/*z*): Calc. = 528.2, Found = 528.2.

*2.2.41. 2-(4-Benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazol-3-yl)-7-methyl-4H-chromen-4-one (**11**)*

Compound **10** of 0.528 g (1 mmole) was dissolved in concentrated H_2SO_4 (2 mL). The reaction was stirred for 6 h at rt. After TLC monitoring, water (10 mL) was added partly to the mixture on ice bath. The formed precipitated product was filtered and the crude product was from ethanol by crystallization. (0,3 g, 75%), mp 215 °C; IR (ν, cm^{-1}): 3060 (aromatic C─H), 2917 (aliph. C─H), 1709 (C═O), 1637 (C═O, benzoyl), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.8–7.0 (m, Ar─H), 6.4 (s, C═CH), 2.1, 1.8 (s, Ar─CH_3), 1.1 (s, Ph─CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 196.34 (C═O, benzoyl), 173.10 (C═O), 158.35, 146.28 (C_3), 143.35 (C_5), 143.13, 140.35, 135.61, 135.37, 132.82, 131.53, 131.19, 130.21, 129.61, 129.32, 129.10, 128.82, 128.44, 127.95, 126.62, 109.0 (C_4), 29.70 (CH_3), 23.03, 18.79 (Ar─CH_3), MS (*m*/*z*): Calc. = 510.19, Found = 510.2.

*2.2.42. 1-(2,5-Dimethylphenyl)-5-phenyl-1H-pyrazole-3,4-diyl)-(bisphenylmethanone) (**12**)*

Compound **12** can be synthesized in two different methods.

Method A: Compound **2a** of 0.414 g (1 mmole) was dissolved in dry benzene and 0.33 g (2.5 mmole) $AlCl_3$was added to this solution. After cooling down of mixture which was refluxed for 3 h, organic phase was separated by adding some ether and ice water. Then ether was evaporated and the residue solid was crystallized from n-hexane/ether (0.27 g, 41%).

Method B: Compound **6** of 0.372 g (1 mmole) was dissolved in dry benzene and 0.33 g (2.5 mmole) $AlCl_3$ was added to this solution. After cooling down of mixture which was refluxed for 3 h, organic phase was separated by adding some ether and ice water. Then ether was evaporated and the residue solid was crystallized from n-hexane/ether. (0.2 g, 30%), mp 292 °C; IR (ν, cm^{-1}): 3057, 3028 (aromatic C─H), 2923 (aliph. C─H), 1707 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67–6.52 (m, 18H, Ar─H), 2.06, 1.83 (s, 3H, Ar─CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.42, 189.38 (C═O, benzoyl), 145.24 (C_3), 144.55 (C_5), 140.66, 139.37, 138.39, 136.26, 133.74, 132.82, 131.41, 130.65, 129.73, 129.26, 129.09, 128.54, 128.37, 127.61, 127.43, 126.35, 109.24 (C_4), 21.31, 17.56 (Ar─CH_3). Anal. Cal. for $C_{31}H_{24}N_2O_2$ (456,53 g/mol): C, 81.56; H, 5.30; N, 6.14. Found: C, 81.50; H, 5.28; N, 6.19.

*2.2.43. 2-(2,5-Dimethylphenyl)-3,4,7-triphenyl-2H-pyrazolo[4,3-d]pyridazine (**13**)*

Compound **12** 0.456 g (1 mmole) was dissolved in dry toluene and 0.032 g (1 mmole) anhydrous hydrazine was added and refluxed for 5 h. Then, solvent was evaporated and 10 mL ether was added to residue product and stirred for an hour. Precipitated product was filtered and purified from ether/chloroform mixture by crystallization. (0,27 g, 70%), mp 241 °C; IR (ν, cm^{-1}): 3030 (aromatic C─H), 2945 (aliph. C─H), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.76–6.38 (m, 18H, Ar─H), 2,06, 1.75 (s, 3H, Ar─CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 164.71 (C_7), 160.43(C_4), 148.68 (C-7a), 146.35 (C_3), 143.24, 141.52, 136.45, 135.07, 134.63, 133.89, 133.40, 132.21, 131.32, 130.91, 130.66, 130.15, 129.72, 129.31, 129.02, 128.80, 128.34, 128.09, 127.63, 127.47, 127.15, 109.12 (C-3a), 21.73, 18.86 (Ar─CH_3), MS (*m*/*z*): Calc. = 452.2, Found = 452.2.

*2.2.44. 2-(2,5-Dimethylphenyl)-3-phenyl-5,6-dihydro-2H-pyrazolo[4,3-d] pyridazine-4,7-dione (**14**)*

Compound **7a** 0.336 g (1 mmole) was dissolved in 10 mL dry toluene and anhydrous hydrazine was added at 1/1 mol rate. The mixture was refluxed for about 5 h. Precipitate white product was filtered and purified from n-hexane/chloroform mixture by crystallization. (0,2 g, 51%), mp 320 °C; IR (ν, cm^{-1}): 3254(N─H), 3026 (aromatic C─H), 2947 (aliph. C─H), 1656 (C═O, amide), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 9.30, 9.13 (b, 1H, NH), 7.85–7.45 (m, 8H, Ar─H), 2.28, 1.80 (s, 3H, Ar─CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 165.49 (C_7), 163.50 (C_4), 145.21 (C-7a), 145.21 (C_3), 144.38 (C_4), 143.76, 136.27, 135.89, 132.64, 130.41, 129.73, 128.36, 127.48, 126.25 (C-3a), 22.15, 17.63 (Ar─CH_3), MS (*m*/*z*): Calc. = 332.1, Found = 332.1.

*2.2.45. 2-(2,5-Dimethylphenyl)-3-phenyl-2H-pyrazolo[4,3-d] pyridazine-4,7-diamine (**15**)*

Compound **8c** 0.372 g (1 mmole) was dissolved in 10 mL anhydrous ethanol. 0.016 g (0.5 mmole) anhydrous hydrazine was added and refluxed for 5 h. The solvent was evaporated and residue compound was washed with ether and water. The crude product was from ethanol by crystallization. (0,22 g, 75%), mp > 320 °C; IR (ν, cm^{-1}): 3324 (─NH_2), 3058 (aromatic C─H), 2922 (aliph. C─H), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.18–6.35 (m, 8H, Ar─H), 4.89, 4.72 (C─NH), 2.28, 1.81 (s, 3H, Ar─CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 163.34 (C_7), 163.15 (C_4), 145.54 (C-7a), 144.39 (C_3), 136.09

(C-3a), 135.43, 133.34, 132.61, 130.34, 129.51, 129.12, 128.35, 127.54, 126.45, 114.18 (C-3a), 18.79, 17.21 (Ar—CH_3). Anal. Cal. for $C_{19}H_{18}N_6$ (330,39 g/mol): C, 69.07; H, 5.49; N, 25.44. Found: C, 68.98; H, 5.51; N, 25.51.

*2.2.46. 2-(2,5-Dimethylphenyl)-3,4-diphenylpyrazolo[4,3d][1,2]oxazin-7(2H)-one (**16**)*

Compound **1a** 0.199 g (0.5 mmole) and excess of hydroxyl amine were heated 150 °C on an oil for 1 h. After cooling to room temperature, the resulting mixture was first washed with water then treated with ether and the formed precipitated product was filtered and the crude product was from n-hexane/chloroform by crystallization. (0.15 g, 65%), mp 130 °C; IR (ν, cm^{-1}): 3057 (aromatic C—H), 2925 (aliph. C—H), 1684 (C_7), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.7–6.5 (m, 13H, Ar—H), 2.19, 1.72 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 164.61 (C_7), 162.13 (C_4), 144.21 (C_3), 141.39 (C_5), 137.12, 133.62, 131.52, 130.56, 130.21, 129.80, 129.14, 128.79, 126.32, 121.12, 109.15 (C-3a), 22.70, 17.09 (Ar—CH_3). Anal. Cal. for $C_{25}H_{19}N_3O_2$ (393,44 g/mol): C, 76.32; H, 4.87; N, 10.68. Found: C, 76.26; H, 4.86; N, 10.77.

*2.2.47. 4-Benzoyl-1-(2-carboxy-5-methylphenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (**17**)*

Compound **1a** of 0.397 gr (1 mmole) was transferred to a flask. 0.524 g (2 mmole) $Na_2Cr_2O_7$ and 1,5 mL water were added the mixture was stirred at room temperature by an hour, 3 drops of 10 to 12 times with an interval of 15 min was added H_2SO_4 and mixed for 24 h and water was added. Then the crude precipitate was isolated by filtration and crystallized from DMSO to give 0.46 g (70%) of **17**, mp 217 °C; IR (ν, cm^{-1}): 3391 (b, —OH), 3051 (aromatic C—H), 2922 (aliph. C—H), 1713 (—OH, COOH), 1663 (C═O, benzoyl), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.2 (b, 1H, —OH), 7.9–6.5 (m, 13H, Ar—H), 1.81 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 191.44 (C═O, benzoyl), 162.74, 160.02 (C═O, acide), 144.73 (C_3), 144.39 (C_5), 139.90, 138.52, 137.30, 136.65, 135.48, 134.81, 132.80, 132.53, 129.66, 129.45, 129.13, 128.41, 127.38, 127.12, 125.32, 121.97 (C_4), 18.84 (Ar—CH_3). Anal. Cal. for $C_{25}H_{18}N_2O_5$ (426,42 g/mol): C, 70.42; H, 4.25; N, 6.57. Found: C, 70.34; H, 4.24; N, 6.67.

*2.2.48. 2-(2,5-Dimethylphenyl)-3-phenyl-2H-furo[3,4-c]pyrazole-4,6-dione (**18**)*

Compound **5** of 0.336 g (1 mmole) was dissolved in a mixture of DMF (0.3 mL) and $SOCl_2$ (1.4 mL) and the reaction was stirred at 0–5 °C for 4 h. After heating to room temperature, stirring was continued overnight, then the reaction mixture was poured over crushed ice and the separated solid isolated by filtration, washed with water and crystallized from ethanol to give 0.18 g (49%), mp 170 °C; IR (ν, cm^{-1}): 3025 (aromatic C—H), 2921 (aliph. C—H), 1684 (C_4, C_6 assoc.), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71–7.05 (m, 8H, Ar—H), 2.32, 1.89 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.32 (C_4), 164.55 (C_6), 144.16 (C_3), 142.83 (C_5), 133.42, 132.36, 131.73, 130.92, 129.78, 129.15, 128.55, 128.22, 127.93, 126.88, 110.12 (C-3a), 23.24, 18.77 (Ar—CH_3), MS (*m*/*z*): Calc. = 318.1, Found = 318.1.

*2.2.49. 2-(2,5-Dimethylphenyl)-3-phenylpyrrolo[3,4-c]pyrazole-4,6(2H,5H)-dione (**19a**)*

Compound **18** of 0.159 g (0.5 mmole) was dissolved in 20 mL ethanol and 0.019 mL (1 mmole) ammonia was added to the reaction pot and refluxed for 48 h. The solvent was evaporated and residue compound was washed with ether and the formed precipitated product was filtered and the crude product was from ethanol by crystallization (0,13 g, 75%), mp 230 °C; IR (ν, cm^{-1}): 3310 (N—H), 3053–3025 (aromatic C—H), 2917 (aliph. C—H), 1661 (C_4, C_6), ^{1}H NMR (400 MHz, DMSO) δ (ppm): 10.01 (s, 1H, NH), 8.07–6.42 (m, 8H, Ar—H), 1.86, 1.28 (s, 3H, Ar—CH_3), ^{13}C NMR (100 MHz, DMSO) δ (ppm): 168.24 (C_6), 165.30 (C_4), 144.51 (C_3), 142.14 (C_5), 137.41, 135.13, 133.35, 131.41, 130.41, 129.82, 129.69, 128.55, 127.26, 125.37, 112.71 (C-3a), 23.30, 20.51 (Ar—CH_3), MS (*m*/*z*): Calc. = 317.1, Found = 317.1.

*2.2.50. 2-(2,5-Dimethylphenyl)-5-ethyl-3-phenylpyrrolo[3,4-c]pyrazole-4,6(2H,5H)-dione (**19b**)*

Compound **18** of 0.159 g (0.5 mmole) was dissolved in 20 mL ethanol and 0.045 g (1 mmole) ethyl amine was added to the reaction pot and refluxed for 48 h. The solvent was evaporated and residue compound was washed with ether and the formed precipitated product was filtered and the crude product was from ethanol by crystallization. (0,15 g, 74%), mp 230 °C; IR (ν, cm^{-1}): 3000 (aromatic C—H), 2914 (aliph. C—H), 1700 (C_4, C_6), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07–6.43 (m, 8H, Ar—H), 4.26 (q, 2H, CH_2), 2,33, 1.76 (s, 3H, Ar—CH_3), 1.35 (t, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 167.29 (C_6), 164.35 (C_4), 143.57 (C_3), 141.04 (C_5), 137.12, 135.30, 133.38, 131.36, 130.24, 130.09, 129.71, 129.36, 128.70, 125.81, 109.41 (C-3a), 51.32 (CH_2), 20.13, 17.80 (Ar—CH_3), 13.50 (CH_3), MS (*m*/*z*): Calc. = 345.1, Found = 345.1.

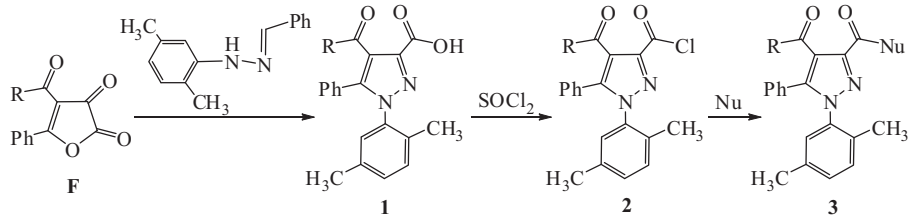
3. Results and discussion

3.1. Chemistry

4-Acyl-pyrazole-3-carboxylic acids **1a,b**, which were our starting compounds, were synthesized via the reaction of furandiones **F** with hydrazone (1-benzylidene-2-(2,5-dimethylphenyl)-hydrazine) by heating in without any solvent media, and its acid chlorides **2a,b** were obtained absolutely. Then these novel derivatives were converted into the corresponding derivatives such as the ester, ureid and amide (Scheme 1). In addition, the other pyrazole derivatives that were outlined in the Scheme 1 were obtained with miscellaneous reactants under mild reaction conditions. All newly synthesized compounds were confirmed by spectroscopic methods which are in agreement with our previous findings [52].

Pyrazole-3-carbonyl-urea derivatives **3 g,h,i,s,t,u** were synthesized by means of the reaction between acid chlorides **2a, b** and urea derivatives in the usual way [51]. Moreover, thioureide derivatives **3 k,l** were prepared by two chemical procedures, both the reaction of the amine derivatives (NH_3, Et-NH_2) with pyrazole-3-carbonyl isothiocyanate **3j** and the reaction of the acid chloride **2a** with thiourea derivatives.

In the case of pyrazole-3-carbonyl isothiocyanate **3j**, the correct structure was established by ^{13}C NMR spectroscopy



F, 1, 2	R
a	-Ph
b	-OEt

3	R	Nu
a	-Ph	$-OCH_3$
b	-Ph	-OEt
c	-Ph	$-NH_2$
d	-Ph	-NH-Ph
e	-Ph	$-NH-Ph(SO_3H)(4)$
f	-Ph	$-NH-NH-Ph(SO_3H)(4)$
g	-Ph	$-NH-CO-NH_2$
h	-Ph	$-NH-CO-NH-CH_3$
i	-Ph	-NH-CO-NH-Ph
j	-Ph	-NCS
k	-Ph	$-NH-CS-NH_2$
l	-Ph	-NH-CS-NH-Et

3	R	Nu
m	-OEt	$-OCH_3$
n	-OEt	-OEt
o	-OEt	$-NH_2$
p	-OEt	-NH-Et
r	-OEt	-NH-Ph
s	-OEt	$-NH-CO-NH_2$
t	-OEt	$-NH-CO-NH-CH_3$
u	-OEt	-NH-CO-NH-Et

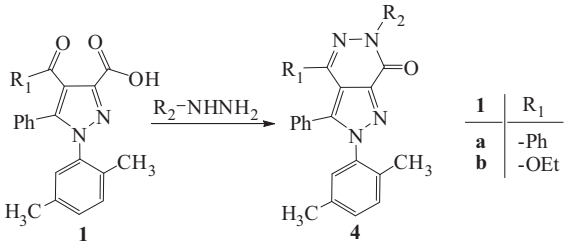
3j $\xrightarrow{R_1-NH_2}$ 3k, l R_1 = H-, Et-

Scheme 1 The ester, ureid and the amide derivatives of pyrazole-carboxylic acids **1a,b**.

in which characteristic C═O peaks were observed at δ 190, 183 ppm and N═C═S peak was observed at δ 147 ppm.

Pyrazole ring which has functional group such as carbonyls, esters, carboxylic acids and nitriles in the vicinal positions is a convenient starting material for further reactions of pyrazole to build the pyrazolo[3,4-d]pyridazine system [51]. The pyrazole acids **1a,b** were cyclized with variable hydrazines to yield pyrazolo[3,4-d]pyridazinone derivatives **4a-n** (Scheme 2). Structure elucidations of **4a-n** are mainly based upon ^{13}C NMR spectroscopy. Signals of carbon atoms of the pyrazolo-pyridazine rings are assigned at about ~160.0 (C-7), ~145.0 (C-7a), ~143.0 (C-3), ~140.0 (C-4) and ~110.0 (C-3a) ppm.

5-Phenyl-1-(2,5-dimethyl-phenyl)-*1H*-pyrazole-3,4-dicarboxylic acid **5** that is the main output compound was prepared from the basic hydrolysis of **1b** in high yield (85%). The structure of **5** was clarified with two carboxylic acid proton signals at δ 10.37 and δ 9.88 ppm, and two carbonyl carbon signals at



1	R_1
a	-Ph
b	-OEt

4	R_1	R_2
a	-Ph	-Ph
b	-Ph	-H
c	-Ph	$-Ph(CH_3)_2(2,5)$
d	-Ph	$-Ph(CH_3)_2(3,4)$
e	-Ph	$-Ph(NO)_2(2,4)$
f	-Ph	$-Ph(Cl)_3(2,4,6)$
g	-Ph	$-Ph(CF_3)(4)$

4	R_1	R_2
h	-OEt	-Ph
i	-OEt	-H
j	-OEt	$-Ph(CH_3)_2(2,5)$
k	-OEt	$-Ph(CH_3)_2(3,4)$
l	-OEt	$-Ph(NO)_2(2,4)$
m	-OEt	$-Ph(Cl)_3(2,4,6)$
n	-OEt	$-Ph(CF_3)(4)$

Scheme 2 Cyclization of pyrazolo[3,4-d]pyridazinone derivatives.

δ 167.8 and δ 164.6 ppm and the characteristic IR absorption bands at 3392–2600 cm^{-1} (COOH), 3058, 3022 cm^{-1} (Ar—C—H), 1716, 1670 cm^{-1} (acid, C═O).

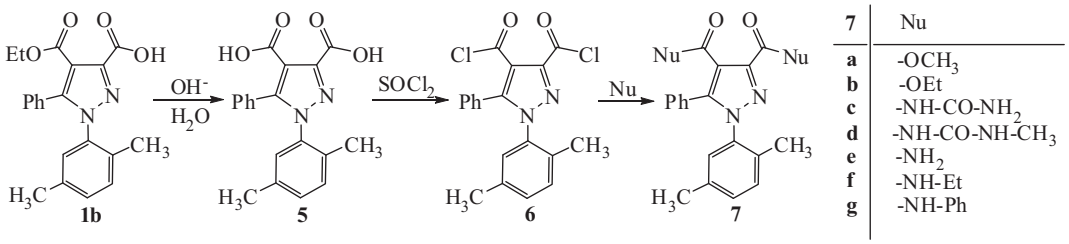
All ester derivatives (**3a**, **3b**, **3m**, **3n**, **7a**, **7b**) of this study were obtained in two different methods which are the Schotten-Baumann and Fischer esterification. Diamide and diureide derivatives **7c–g** were obtained via reactions of **6** with various amine and urea derivatives (Scheme 3).

The pyrazolo-carbodiamide **7e** and pyrazolo-carboamide **3c, 3o** derivatives were treated with a mixture of DMF and $SOCl_2$ at −5 °C for 2 h to give pyrazolo-carbonitrile **8** derivatives (Scheme 4). Characteristic ^{13}C NMR and IR signal of the nitrile group(s) in **8a–c** are found at 107–116 ppm and 2162–2207 cm^{-1}, respectively (see Experimental).

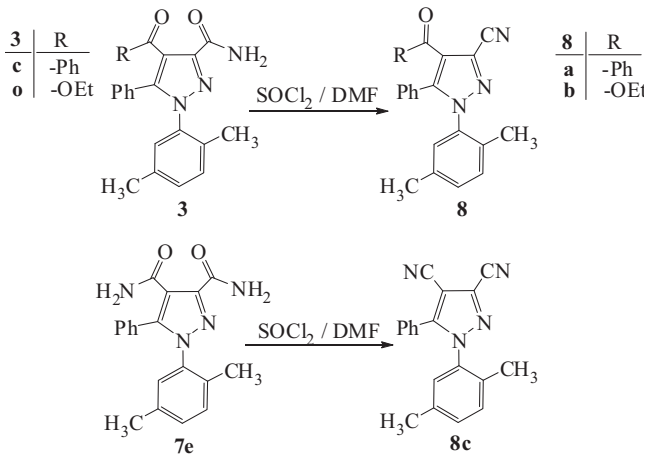
Regio-specific decarboxylation of **5** at high temperature (200 °C) revealed that nitrogen atom of pyrazole adjacent to carbon atom is a driving force for decarboxylation probably due to the hydrogen bonding between lone pair of nitrogen and hydrogen atom of the carboxylic acid. The formation of decarboxylated pyrazole **9c** was confirmed by basic hydrolysis of **9b** followed by decarboxylation of **1b** (Scheme 5) [59].

One of the most important examples for further derivatization of 4-acyl-pyrazolo-3-carboxylic acids which includes the reactions of corresponding pyrazolo-3-carbonyl chloride with 4-methyl-2-hydroxy-acethophenone in basic media was reported by our research group [60]. The mechanistic details of rearrangement reaction were displayed in our former study. To repeat this reaction with a new pyrazole acid, **2a** was reacted with 4-methyl-2-hydroxy-acethophenone under basic condition at room temperature. Forming of **10** was explained with Baker–Venkataraman rearrangement in one-pot as an instance of domino reaction [61]. Further reaction of **10** included the cyclization to obtain pyrazol-3-methyl-4H-chromen **11** after removing H_2O using H_2SO_4 (See Scheme 6).

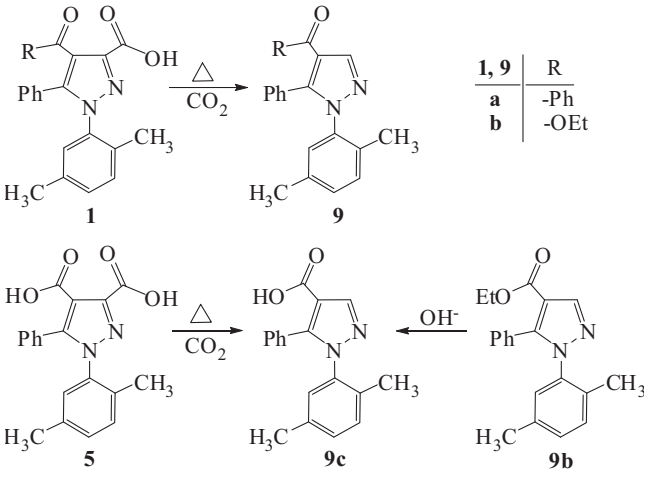
On the other hand, 3,4-dibenzoyl-pyrazole **12** was synthesized from two different compounds by Friedel–Crafts acylation. Refluxing of corresponding derivatives **2a** and **6** in dry benzene with $AlCl_3$ as catalyst resulted in the formation of



Scheme 3 Pyrazole-3,4-dicarboxylic acid and further derivatives.



Scheme 4 Synthetic route of pyrazolo-carbo(di)nitrile derivatives.



Scheme 5 Decarboxylation of synthesized carboxylic acids.

12. In continuation of the reaction, 3,4-dibenzoyl-pyrazole **12** was cyclized using anhydrous hydrazine to furnish pyrazolo [4,3-d]pyridazine **13** (Scheme 7).

Pyrazolo-pyridazine derivatives have shown biological activities such as antimicrobial, antiinflammatory and analgesic activities [62]. Therefore, in addition to **4**, we synthesized various derivatives of pyrazolo-pyridazine **13**, **14**, **15** by several different methods (Scheme 8). Reaction of **7a** with anhydrous hydrazine in dry toluene led to the formation of the 2-(2,5-di methylphenyl)-3-phenyl-5,6-dihydro-2H-pyrazolo[4,3-d]pyridazine-4,7-dione **14**. Structure of this compound was confirmed with spectral data especially mass spectrum (See Experiments). The mass spectra showed the presence of molecular ion peak M^+ at *m/e* 332.1. Furthermore, as a result of cyclization of pyrazole-3,4-dicarbonitrile **8c** under reflux condition of ethanol with anhydrous hydrazine, 4,7-diamino-pyrazolo[3,4-*d*] pyridazine **15** occurred at 75% yield (Scheme 8). Structure elucidation of **15** is mainly based on ^{13}C NMR spectroscopy. Peaks at 163.34 (C-7), 163.15 (C-4), 145.54 (C-7a) and 114.18 (C-3a) ppm are assigned to carbon atoms of the pyridazine ring of **15**.

Reaction of the acid **1a** with excess hydroxylamine hydrochloride under solid phase, inside an oil-bath at approximately 150–155 °C led to the formation of the pyrazolo[4,3-*d*] oxazinone **16** (Scheme 9). Confirming of structure of **16** is based on particularly elemental analysis and the other spectral data (see Experimental).

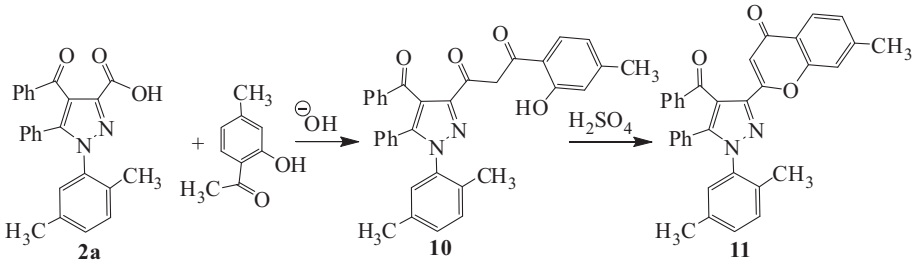
Methyl groups at benzene ring were subjected to oxidize to reach another carboxylic acid group which might give more soluble pyrazole in water. To serve this purpose, oxidizing reagent, $Na_2Cr_2O_7$, was applied and surprisingly, it was observed that only one methyl group was oxidized. According to chemical shift of functional groups, we found out that *orto*-substituted methyl group was only oxidized to carboxylic acid [63]. This might be because of the facts that free lone pair of nitrogen atom close to the ortho-methyl group serves as a ligand for metal (Scheme 9).

As a result of dehydration of **5** in DMF/$SOCl_2$ at −5 °C, furo[3,4-c]pyrazole-4,6-dione **18** compound was occurred at 49% yield. This compound is remarkably stable (mp 170 °C) and the structure of **18** obtained in this way was confirmed by analytical and spectral data (see experimental). In the mass spectra, molecular ion peak M^+ appeared at *m/e* 318.1 (75%).

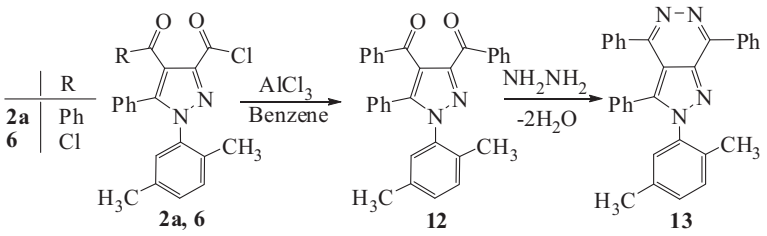
Moreover, furandione ring in compound **18** was converted into pyrrolo[3,4-c]pyrazoledione derivatives **19** via a reaction with ammonia and ethyl amine in ethanol. This type of heterocyclic ring is not found in the literature interested in 4-acyl-pyrazole derivatives so far. Structure elucidation of these compounds were done by spectroscopic data (**18** *m/e*: 317.1 (50%), **19** *m/e*: 345.1 (75%)) (Scheme 10).

3.2. Biological evaluation (antibacterial activities)

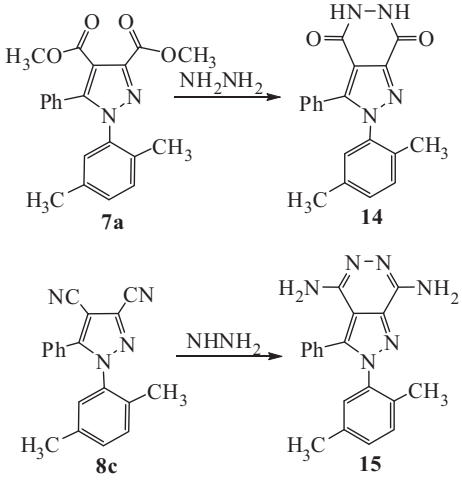
The *in vitro* antibacterial activities of novel synthesized compounds were determined against gram-positive bacteria including *Bacillus subtilis* and *Staphylococcus aureus* and gram-negative bacteria including *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* via using well diffusion method (zone inhibition) [64,65]. Briefly, a bacterial suspension was added to sterile nutrient agar at 45 °C and the mixture



Scheme 6 Synthesis of pyrazol-3-methyl-4H-chromen **11.**



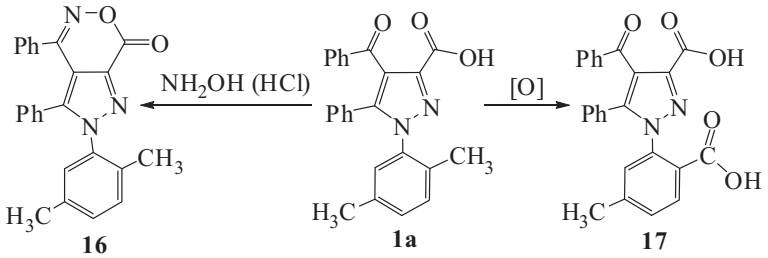
Scheme 7 Further reactions for pyrazolo-carbonyl chloride **2a** and **6**.



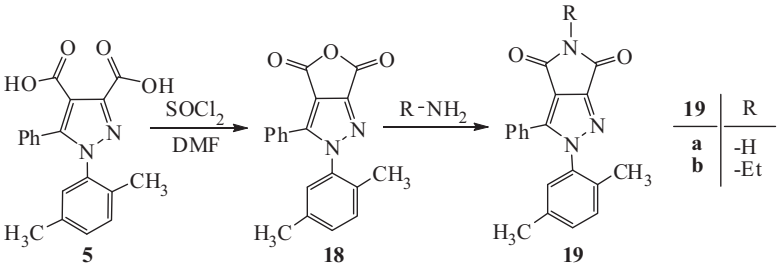
Scheme 8 Formation of new pyrazolo-pyridazine derivatives via different compounds.

was poured into Petri dish on a horizontally levelled surface. After the medium was solidified, wells of dish were made in the agar medium. Subsequently 25 µl, 50 µl, and 100 µl of the newly synthesized compounds suspensions were loaded into the wells separately. The Petri dishes were incubated at 37 °C for 1 day in an oven. Experiments were carried out in triplicate and average zone diameters were measured. Compounds showing growth inhibition zones (⩾9 mm) were replicated using the two fold serial dilution technique. *Erythromycin* (15 mg), *Rifampicin* (5 mg) and *Amikacin* (10 mg) antibiotics were used as positive control. Dimethylsulfoxide was used as control and no visible inhibition zone was observed on control groups. The solutions of all compounds were prepared in double distilled water.

As presented in Table 1, some of the newly synthesized compounds showed the minimal inhibitory concentrations (MIC, µg/mL) and inhibition zone (mm) against all the screened gram-positive bacteria and gram-negative bacteria. It can be seen on Fig. 2 that some of the compounds **2a, 4a, 4e, 4f, 4g, 3e, 3g, 3i, 2b, 4h, 4m, 4n, 4l, 8b, 19a, 19b** showed higher activity than *Amikacin* against *S. aureus* (MIC, 25–100 µg/mL). Compounds **2a, 2b, 4a, 4b, 4c, 4d, 4h, 4m, 4n, 6, 7f, 15, 19a, 19b** displayed higher antimicrobial activities than *Rifampicin* (reference drug) against the *P. aeruginosa* bacteria (Fig. 3). Compounds **2a, 4a** and **4l** exhibited more inhibitory activities than *Amikacin* against *K. Pneumonia,* a gram-negative bacterium (MIC 100 µg/mL) among all compounds tested. On the other hand, compounds **2a, 3e, 3f, 4f, 4g, 4m** and **4n** exhibited more inhibitory activities than *Amikacin*



Scheme 9 Further reactions of the pyrazole-acid **1a**.



Scheme 10 Embodiment of furo[3,4-c]pyrazole **18** and pyrrolo[3,4-c]pyrazole **19**.

Table 1 Minimal inhibitory concentrations (MIC, μg/mL) and inhibition zone (mm) of some new synthesized compounds.

Compound No	MIC[a] in μg/mL and zone of inhibition (mm)				
	Bacteria				
	Gram-positive bacteria		Gram-negative bacteria		
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumonia*
1a	100 (9)	100 (9)	–[b]	–	–
2a	50 (12)	100 (11)	50 (10)	25 (10)	100 (11)
2b	50 (11)	100 (10)	100 (10)	50 (9)	50 (10)
3e	50 (13)	100 (10)	100 (10)	–	50 (10)
3f	100 (12)	50 (10)	50 (10)	–	50 (10)
3h	100 (10)	–	–	–	–
3i	100 (10)	100 (10)	100 (9)	–	50 (9)
3j	100 (9)	100 (9)	50 (9)	–	–
3k	100 (9)	–	100 (9)	–	–
3l	100 (9)	–	100 (9)	–	–
4a	50 (10)	50 (10)	50 (9)	100 (9)	100 (11)
4b	100 (10)	50 (9)	–	50 (9)	50 (9)
4c	50 (9)	50 (9)	50 (10)	50 (9)	–
4d	50 (9)	50 (9)	50 (10)	50 (9)	–
4e	25 (11)	50 (11)	50 (11)	–	–
4f	50 (14)	50 (11)	25 (10)	–	50 (9)
4g	25 (13)	50 (12)	50 (10)	–	50 (9)
4h	50 (10)	50 (10)	50 (9)	50 (10)	50 (9)
4m	25 (13)	50 (13)	50 (12)	50 (10)	100 (10)
4n	25 (13)	50 (12)	50 (11)	100 (9)	50 (10)
4l	50 (11)	100 (11)	50 (11)	100 (10)	100 (11)
6	100 (10)	50 (9)	100 (12)	100 (9)	50 (9)
7e	100 (10)	–	–	–	–
7f	100 (11)	–	–	100 (9)	–
7g	100 (10)	100 (9)	50 (9)	–	–
8a	100 (10)	–	–	–	100 (9)
8b	100 (9)	50 (10)	–	–	100 (9)
8c	100 (9)	–	100 (9)	–	100 (9)
9c	100 (9)	–	–	–	–
10	50 (10)	100 (9)	–	–	–
12	50 (9)	–	100 (10)	–	50 (9)
15	100 (9)	–	50 (10)	100 (9)	–
16	100 (10)	50 (9)	50 (10)	–	–
17	100 (10)	100 (9)	–	–	–
18	100 (10)	–	–	–	–
19a	100 (11)	50 (10)	50 (11)	50 (10)	50 (9)
19b	100 (11)	100 (10)	50 (11)	100 (10)	50 (9)
Ref. drugs					
Erythromycin	100 (20)	100 (21)	100 (19)	100 (19)	100 (19)
Rifampicin	100 (21)	100 (18)	100 (18)	100 (8)	100 (19)
Amikacin	100 (11)	100 (9)	100 (13)	100 (14)	100 (10)

[a] MIC: Minimal inhibitory concentration values with SEM = 0,02.
[b] (–): Totally inactive (no inhibition).

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008

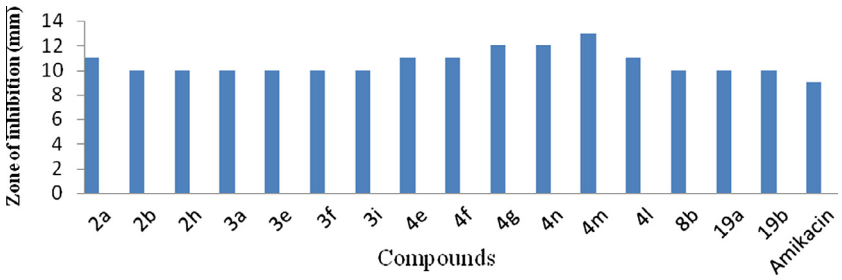


Figure 2 Antibacterial activity of against *Staphylococcus aureus* bacteria.

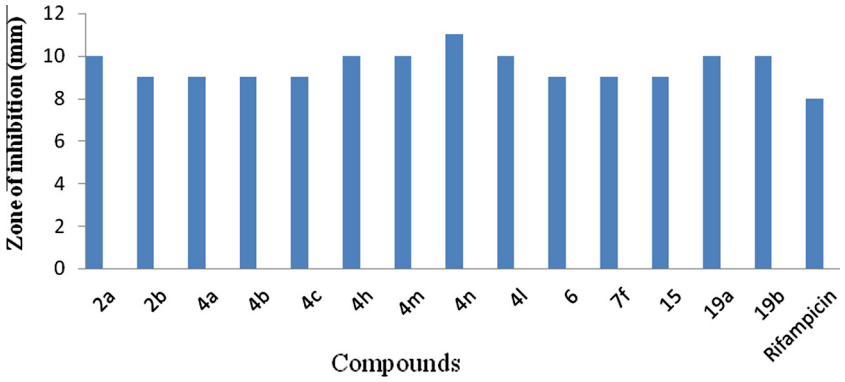


Figure 3 Antibacterial activity of against *Pseudomonas aeruginosa* bacteria.

against *B. subtilis,* gram-positive bacteria. Also reference drugs showed more inhibitory activities than all of the newly synthesized compounds against *E. coli* bacteria. Additionally, *Erythromycin* showed more inhibitory activity than all of the newly synthesized compounds against all tested organisms. On the other hand, compounds **2b, 3t, 4e, 4l, 19a** and **19b** were equipotent to *Amikacin* in inhibiting the growth of *B. subtilis*. Also compounds **2b**, **3e, 3f, 4m** and **4n** were equipotent to *Amikacin* in inhibiting the growth of *K. pneumonia*.

Finally, it can be suggested that these newly synthesized compounds might have potential antibacterial activity owing to containing pyrazole, pyridazine, oxazine and pyrrole rings. Besides among these series, some compounds that contain chlorine, fluorine groups at different position to the phenyl ring showed similar activities compared to the reference drugs. The compounds containing electron withdrawing substituents at different position such as chlorine and fluorine showed good activity against *P. aeruginosa* and *S. Aureus*. Our results indicate that substituents containing different groups such as chlorine, fluorine, methyl and NO_2 are able to increase the biological activities of compounds. In conclusion, the substituted pyrazoles showed a wide variety of biological and pharmacological activities and might have a wide application both in pharmaceuticals and in the agricultural industry. Therefore, the methods developed for the synthesis of these compounds are becoming more important.

4. Conclusions

We have gathered a lot of new derivatives of 4-acyl-pyrazole in a single work. All of our synthesized compounds have one or two important rings and so, we think that these derivatives may occupy a vital place in pharmaceutical fields. Besides, according to the *in vitro* studies, some of our promising compounds might be new candidates as new generation antibacterial drugs.

Declaration of interest

The authors report no declarations of interest.

Acknowledgments

The authors are indebted to the Scientific Research Projects Chairmanship (BAP) of Yuzuncu Yil University for its financial support of this study. Project Number: 2011-FBE-D006.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2016.05.008.

References

[1] İ. Bildirici, A. Şener, İ. Tozlu, Further derivatives of 4-benzoyl-1, 5-diphenyl-1H-pyrazole-3-carboxylic acid and their antibacterial activities, Med. Chem. Res. 16 (2007) 418–426.
[2] V. Lee, S.J. Hecker, Novel antitumor agents from higher plants, J. Med. Res. Rev. 19 (1999) 521–542.
[3] W.S. Sung, H.J. Jung, K. Park, H.S. Kim, I.S. Lee, D.G. Lee, 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF); antimicrobial compound with cell cycle arrest in nosocomial pathogens, Life Sci. 80 (2007) 586.
[4] S. Fustero, M. Sanchez-Rosello, P. Barrio, A. Simon-Fuentes, From 2000 to Mid-2010: a fruitful decade for the synthesis of pyrazoles, Chem. Rev. 111 (2011) 6984–7034.

[5] H.S. Ibrahim, S.M. Abou-Seri, M. Tanc, M.M. Elaasser, H.A. Abdel-Aziz, C.T. Supuran, Isatin-pyrazole benzenesulfonamide hybrids potently inhibit tumor-associated carbonic anhydrase isoforms IX and XII, Eur. J. Med. Chem. 103 (2015) 583–593.
[6] T.S. Reddy, H. Kulhari, V.G. Reddy, V. Bansal, A. Kamal, R. Shukla, Design, synthesis and biological evaluation of 1, 3-diphenyl-1H-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents, Eur. J. Med. Chem. 101 (2015) 790–805.
[7] Ş.G. Küçükgüzel, S. Şenkardeş, Recent advances in bioactive pyrazoles, Eur. J. Med. Chem. 97 (5) (2014) 786–815.
[8] D. Raffa, B. Maggio, M.V. Raimondi, S. Cascioferro, F. Plescia, G. Cancemi, G. Daidone, Recent advanced in bioactive systems containing pyrazole fused with a five membered heterocycle, Eur. J. Med. Chem. 97 (5) (2014) 732–746.
[9] İ. Bildirici, A. Şener, E. Atalan, A.H. Battal, H. Genç, Synthesis and antibacterial activity of 4-benzoyl-1-(4-carboxy-phenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid and derivatives, Med. Chem. 18 (2009) 327–340.
[10] N. Srikantamurthy, K.B. Umesha, D.D. Shridevi, K. Shulbakara, J. Chethan, Novel pyrazole integrated 1,3,4-oxadiazoles: synthesis, characterization and antimicrobial evaluation, Bioorg. Med. Chem. 24 (1) (2014) 245–248.
[11] R.N. Mahajan, F.H. Havaldar, P.S. Fernandes, Syntheses and biological activity of heterocycles derived from 3-methoxy-1-phenyl-1H-pyrazole-5-carboxylate, J. Indian Chem. Soc. 68 (1991) 245.
[12] C.B. Sangani, J.A. Makawana, X. Zhang, L.L. Tereiya, H.L. Zhu, Design and synthesis and molecular modelling of pyrazole-quinoline-pyridine hybrids as a new class of antimicrobial and anticancer agents, Eur. J. Med. Chem. 76 (2014) 549–557.
[13] R. Sridhar, T.P. Paramasivam, E. Sundaresan, S. Guruswamy, N.P. Mondikalipudur, R.P. Vaiyapuri, M. Narayanasamy, Synthesis and anti-microbial activity of 1H-pyrazole Carboxylates, Bioorg. Med. Chem. Lett. 14 (2004) 6035.
[14] N.C. Desai, K.M. Joshi, H.V. Rajpara, H.M. Satodiya, Facilesyntheisi of novel fluorine containing pyrazole based thiazole derivatives and evaluation of antimicrobial activity, J. Fluorine Chem. 142 (2012) 67–78.
[15] G. Sivaprasad, T.P. Paramasivan, R.P. Vaiyapuri, M. Narayanasamy, Synthesis and anti-microbial activity of pyrazolylbisindoles-promising anti-fungal compounds, Bioorg. Med. Chem. Lett. 16 (2006) 6302.
[16] S. Viveka, L.N. Madhu, G.K. Nagaraja, Synthesis of new pyrazole derivatives via multi component reaction and evaluation of their antimicrobial and antioxidant activities, Monatsh. Chem. 1463 (9) (2015) 1547–1555.
[17] P.G. Baraldi, S. Manfredini, R. Romagnoli, L. Stevanato, A.N. Zaid, R. Manservigi, Synthesis and anti-HSV-1 activity of 6 substituted pyrazolo[3,4-d]pyridazin-7-one nucleosides, Nucleosides Nucleotides 17 (1998) 2165.
[18] A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, J.A. Micky, F. M. Abdel-Megeid, Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolo-pyrimidine derivatives, Bioorg. Med. Chem. 16 (15) (2008) 7102–7106.
[19] S.L. Janus, A.Z. Magdif, B.P. Erik, N. Claus, Synthesis of triazenopyrazole derivativesas potential inhibitors of HIV-1, Monatsh. Chem. 130 (1999) 1167.
[20] O.I. El-Sabbagh, M.M. Baraka, S.M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, A.A. Rashad, Synthesis and antiviral activity of new pyrazole and thiazole derivatives, Eur. J. Med. Chem. 44 (9) (2009) 3746–3753.
[21] A. Balbi, M. Anzaldi, C. Macciò, C. Aiello, M. Mazzei, R. Gangemi, P. Castagnola, M. Miele, C. Rosano, M. Viale, Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity, Eur. J. Med. Chem. 46 (2011) 5293–5309.
[22] A. Kamal, A.B. Shaik, N. Jain, C. Kishor, A. Nagabhushana, B. Supriya, S.S. Chourasiya, Y. Suresh, K.R. Mishra, A. Addlaganatta, Design and synthesis of pyrazole–oxindole conjugates targeting tubulin polymerization as new anticancer agents, Eur. J. Med. Chem. 92 (2015) 501–513.
[23] N. Gokhan-Kelekci, S. Yabanoglu, E. Kupeli, U. Salgin, O. Ozgen, G. Ucar, E. Yesilada, E. Kendi, A. Yesilada, A.A. Bilgin, A new therapeutic approach in Alzheimer disease: some novel pyrazole derivatives as dual MAO-B inhibitors and anti-inflammatory analgesics, Bioorg. Med. Chem. 15 (2007) 5775–5786.
[24] E. Badawey, I.M. El-Ashmawey, Nonsteroidal anti-inflammatory agents-Part 1: anti-inflammatory, analgesic and antipyretic activity of some new 1-(pyrimidin-2-yl)-3-pyrazolin-5-ones and 2-(pyrimidin-2-yl)-1,2,4,5,6,7-hexahydro-3H-indazol-3-ones, Eur. J. Med. Chem. 33 (1998) 349.
[25] S.G. Alegaon, K.R. Alagawadi, M.K. Garg, K. Dushyant, D. Vinod, 1, 3, 4-Tri substituted pyrazole analogues as promising anti-inflammatory agents, Bioorg. Chem. 54 (2014) 51–59.
[26] A.K. Tewari, A. Mishra, Synthesis and anti-inflammatory activities of N4, N5-disubstituted-3-methyl-1H-pyrazolo[3,4-c] pyridazines, Bioorg. Med. Chem. 9 (2001) 715–718.
[27] P.D. Mishra, S. Wahidullah, S.Y. Kamat, A heteroaromatic acid from marine sponge Suberites vestigium, Indian J. Chem. Soc. Sec. B 37 (1998) 199.
[28] F. Colliot, K.A. Kukorowski, D.W. Hawkins, D.A. Roberts, Fipronil: a new soil and foliar broad spectrum insecticide, Brighton Crop Prot. Conf. Pests Dis. 1 (1992) 29–34.
[29] H.S. Chen, Z.M. Li, Y.F. Han, Synthesis and fungicidal activity against Rhizoctonia solani of 2-alkyl (alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (thiadiazoles), J. Agric. Food Chem. 48 (2000) 5312–5315.
[30] M. Ramiz, I. Hafiz, S. Abdel, M. Reheim, A.M. Abdel, H.M. Gaber, Pyrazolones as building blocks in heterocyclic synthesis: synthesis of new pyrazolo pyran, pyrazolo pyridazine and pyrazole derivatives of expected antifungicidal activity, J. Chin. Chem. Soc. 59 (1) (2012) 72–80.
[31] C.B. Vicentini, C. Romagnoli, E. Andreotti, D. Mares, Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi, J. Agric. Food Chem. 55 (2007) 10331–10338.
[32] M. Kurowski, A. Dunky, M. Geddawi, Transsynovial distribution and protein binding of pirazolac in patients with rheumatoid arthritis, Eur. J. Clin. Pharmacol. 31 (1986) 307–311.
[33] F. Lepage, B. Hublot, European Patent Application EP 459 887, Chem Abstr. 116 (1992) 128917.
[34] D.M. Bailey, P.E. Hansen, A.G. Hlavac, E.R. Baizman, J. Pearl, A.F. DeFelice, M.E. Feigenson, 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants, J. Med. Chem. 28 (2) (1985) 256–260.
[35] R.H. Wiley, P. Wiley, Pyrazolones, Pyrazolidones and Derivatives, John Wiley and sons, New York, 1964, p. 102.
[36] D. David do CarmoMalvar, R.T. Ferreira, R.A. De Castro, L. L. De Castro, A.C.C. Freitas, E.A. Costa, F.A. Vanderlinde, Antinociceptive, anti-inflammatory and antipyretic effects of 1.5-diphenyl-1H-Pyrazole-3-carbohydrazide, a new heterocyclic pyrazole derivative, Life Sci. 95 (2) (2014) 81–88.
[37] S. Mert, R. Kasımoğulları, T. İça, F. Çolak, A. Altun, S. Ok, Synthesis, structure activity relationships, and in vitro antibacterial and antifungal activity evaluations of novel pyrazole carboxylic and dicarboxylic acid derivatives, Eur. J. Med. Chem. 78 (2014) 86–96.
[38] Y.R. Li, C. Li, J.C. Liu, M. Guo, T.Y. Zhang, L.P. Sun, H.R. Piao, Synthesis and biological evaluation of 1,3-diaryl pyrazole derivatives as potential antibacterial and anti-inflammatory agents, Bioorg. Med. Chem. Lett. 25 (2015) 5052–5057.

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008

[39] N.K. Terrett, A.S. Bell, D.P.B. Ellis, Sildenafil (Viagra TM), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction, Bioorg. Med. Chem. Lett. 6 (1996) 1819–1824.
[40] T.D. Pennig, J.J. Tolley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang, P.C. Isakson, Synthesis and biological evaluation of the 1,5-Diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-Methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib), J. Med. Chem. 40 (1997) 1347–1365.
[41] A. Volonterio, L. Moison, J. Rebek, Synthesis of pyridazine-based scaffolds as α-Helix mimetics, Org. Lett. 9 (2007) 3733–3736.
[42] A.A. Singer, M. Dore, J.E. Sieser, M.A. Berliner, Development of nonproprietary phosphine ligands for the Pd-catalyzed amination reaction, Tetrahedron Lett. 47 (2006) 3727–3731.
[43] A. Porzelle, M.D. Woodrow, N.C.O. Tomkinson, Synthesis of benzoxazolones from nitroarenes or aryl halides, Org. Lett. 11 (2009) 233–236.
[44] S. Fustero, R. Roman, J.F. Sanz-Cervera, A. Simon-Fuentes, J. Bueno, S. Villanova, Improved regioselectivity in pyrazole formation through the use of fluorinated alcohols as solvents: synthesis and biological activity of fluorinated tebufenpyrad analogs, J. Org. Chem. 73 (2008) 3523–3529.
[45] L. Meng, B.A. Lorsbach, T.C. Sparks, J.C. Fettinger, M.J. Kurth, Parallel synthesis of bis-heterocyclic isoxazolylmethyl- and isoxazolinylmethylpyrazoles, J. Comb. Chem. 12 (2010) 129–136.
[46] H.L. Liu, H.F. Jiang, M. Zhang, W.J. Yao, Q.H. Zhu, Z. Tang, One-pot three-component synthesis of pyrazoles through a tandem coupling-cyclocondensation sequence, Tetrahedron Lett. 49 (2008) 3805–3809.
[47] A. Padwa, 1,3-Dipolar Cycloaddition Chemistry, vol. I, John Wiley Sons, New York, 1984.
[48] A. Padwa, W.H. Pearson (Eds.), Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, John Wiley Sons, New York, 2002.
[49] A. Şener, İ. Tozlu, H. Genç, İ. Bildirici, K. Arısoy, Synthesis and some reactions of 4-(Ethoxycarbonyl)-1,5-diphenyl-1H-pyrazole-3-carboxylic acid, J. Heterocycl. Chem. 44 (2007) 1077–1081.
[50] Y. Akçamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E.M. Peters, H.G. Von Schnering, Reaktionen mit cyclischen Oxalylverbindungen, XXIV. Zur Reaktion von 4-Benzoyl-5-phenyl-furan-2,3-dion mit Phenylhydrazonen bzw, Phenylhydrazin Monatsh. Chem. 117 (1986) 231–245.
[51] Y. Akçamur, A. Şener, M. İpekoğlu, G. Kollenz, Functionalization and cyclization reactions of 4-benzoyl-1,5-diphenyl- 1*H*-pyrazole-3-carboxylic acid, J. Heterocycl. Chem. 34 (1) (2009) 221–224.
[52] A. Şener, R. Kasımoğulları, M.K. Şener, İ. Bildirici, Y. Akçamur, Studies on the reactions of cyclic oxalyl compounds with hydrazines or hydrazones: Synthesis and reactions of 4-benzoyl-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid, J. Heterocycl. Chem. 39 (2002) 869–875.
[53] A. Şener, İ. Bildirici, Synthesis and some reactions of 4-benzoyl-5-phenyl-1-(2,4,6-trichloro phenyl)-1H-pyrazole-3-carboxylic acid, Turk. J. Chem. 28 (2004) 149–156.
[54] R.A. Tucaliuc, V.V. Cotea, M. Niculaua, C. Tuchilus, D. Mantu, I.I. Mangalagiu, New pyridazine-fluorine derivatives: synthesis, chemistry and biological activity. Part II, Eur. J. Med. Chem. 67 (2013) 367–372.
[55] F.M. Awadallah, T.A. El-Waei, M.M. Hanna, S.E. Abbas, M. Ceruso, B.E. Oz, O.O. Guler, C.T. Supuran, Synthesis, carbonic anhydrase inhibition and cytotoxic activity of novel chromone-based sulfonamide derivatives, Eur. J. Med. Chem. 96 (2015) 425–435.
[56] R. Kalirajan, V. Kulshrestha, S. Sankar, S. Jubie, Docking studies, synthesis, characterization of some novel oxazine substituted 9-anilinoacridine derivatives and evaluation for their antioxidant and anticancer activities as topoisomerase II inhibitors, Eur. J. Med. Chem. 56 (2012) 217–224.
[57] G. Álvarez, J. Martínez, J. Varela, E. Birriel, E. Cruces, M. Gabay, S.M. Leal, P. Escobar, B. Aguirre-López, N. Cabrera, M.T. Gómez-Puyou, A.G. Puyou, R. Pérez-Montfort, G. Yaluff, S. Torres, E. Serna, N.V. Bilbao, M. González, H. Cerecetto, Development of bis-thiazoles as inhibitors of triosephosphate isomerase from Trypanosoma cruzi. Identification of new non-mutagenic agents that are active in vivo, Eur. J. Med. Chem. 100 (2015) 246–256.
[58] A. Domagala, T. Jarosz, M. Lapkowski, Living on pyrrolic foundations-advances in natural and artificial bioactive pyrrole derivatives, Eur. J. Med. Chem. 100 (2015) 176–187.
[59] R. Kasimogullari, B.S. Arslan, Synthesis and characterization of some pyrazole derivatives of 1,5-diphenyl-1H-pyrazole-3,4-dicarboxylic acid, J. Heterocycl. Chem. 47 (2010), doi:1040-1048.
[60] S. Çam, İ. Bildirici, N. Mengeş, M. Tan, A. Şener, An entry into obtaining pyrazole, chromone or oxadiazole substituted 1H-pyrazoles via 2,3-furandıones, J. Heterocycl. Chem. 50 (2013) 211–216.
[61] A.V. Kalinin, A.J.M. Da Silva, C.C. Lopes, R.S.C. Lopes, V. Snieckus, Tetrahedron Lett. 39 (28) (1998) 4995–4998.
[62] A.K. Tewari, A. Mishra, Synthesis and anti-inflammatory activities of N4, N5-disubstituted-3-methyl-1H-pyrazolo[3,4-c] pyridazines, Bioorg. Med. Chem. 9 (2001) 715–718.
[63] M. Balci, Basic ^{1}H- and ^{13}C NMR Spectroscopy, Elsevier, 2005, ISBN 978-0-444-51811-8.
[64] A.P. David, J.P. McCuen, Manual of BBL Products and Laboratory Procedures, sixth ed., 1988, pp. 67–72, U.S.A..
[65] L.J. Bradshaw, Laboratory Microbiology, fourth ed., Printed in U.S.A., 1992, p. 435.

Please cite this article in press as: A. Çetin, İ. Bildirici, A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles, Journal of Saudi Chemical Society (2016), http://dx.doi.org/10.1016/j.jscs.2016.05.008